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UNUSUAL HISTOLOGICAL APPEARANCES IN DUHRING-BROCQ'S DISEASE.*

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Most authors agree that the most valid criterion of Duhring-Brocq's disease is the histological. However, there is considerable evidence that the subepidermal bulla caused by rapid detachment of the epidermis is not the sole lesion of this disease.

Classical descriptions recorded the possible occurrence of intraepidermal vesicles. A. Civatte (1943, 1949) stressed that the subepidermal bulla constituted the essential lesion of the affection, without which it could not be diagnosed. At the same time, he admitted that in a few cases there sometimes occurred subcorneal vesicles which were always independent of the subepidermal bullae. Percival and Hannay (1949) and Lever (1953) remarked on superficial bullae which they attributed to regeneration of the epidermis, whilst Zilberberg (1955) invoked the more or less sudden outpouring of fluid.

In 1953, van der Meiren and Achten drew attention to the necrosis of malpighian cells which could cause the intra-epidermal bullae which Lapière (1953) had also noted. Nieuwmeyer (1953), Floden and Gentile (1955) and Jarrett (1957) observed the acantholytic phenomena rediscovered by Achten (1956, 1958). Piérard, Dupont and Fontaine (1957, 1958) described changes limited to the herpetiform type of the disease. These consisted of the necrobiosis of the basal and deeper layers of the epidermis, causing a dermo-epidermal split, due to the presence of microabscesses containing polymorphs and eosinophils in the dermal papillae. These microabscesses were absent in the pemphigoid variety and in erythema multiforme.

Having reviewed fifty cases in which the diagnosis of Duhring's disease was certain or probable, we have repeatedly discovered epidermal necrosis, acantholysis, karyolysis, microabscesses in the dermal papillae and fibrinoid necrosis of the superficial dermal collagen. The sub- or intracorneal bullae or pustules particularly claimed our interest.

* Read at the Franco-British Reunion in London, 1960.

INVESTIGATION.

Group I: This was much the most important and comprised cases in which the diagnosis of Duhring's disease was indisputable. In three of them, very superficial bullae were associated with subepidermal detachment (Fig. 1), either in the same sections or in successive biopsy specimens.

Case 1.—A woman aged 44 who had had typical Duhring's disease for six months, herpetiform phases alternating with pemphigoid. There were also lesions in the mouth. One biopsy specimen showed a subepidermal bulla whose roof was necrotic in places, separated by intact epidermis from a superficial intraepidermal bulla of almost identical size, situated at the level of the upper layers of the stratum mucosum

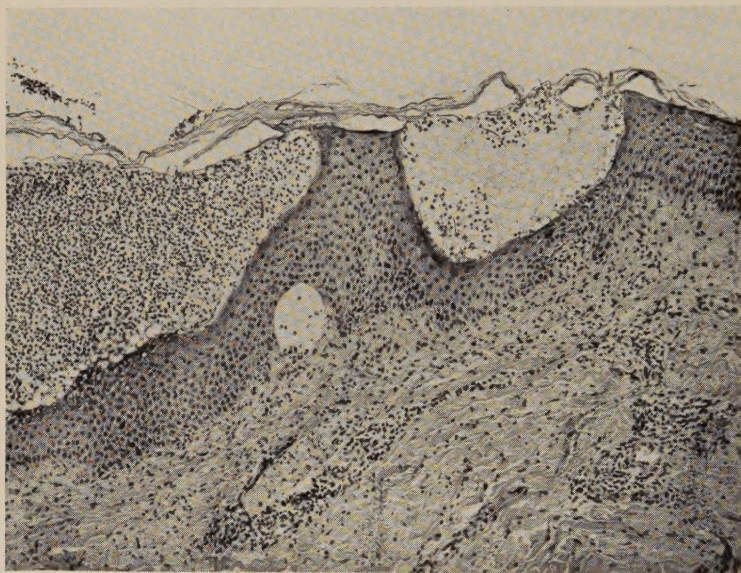


FIG. 1.—Duhring's disease of herpetiform type. In the same preparation there are two subcorneal bullae, one of which contains more fluid than cells, and also a small subepidermal detachment.

and covered with parakeratotic lamellae. The two bullae were filled with serum and polymorphonuclear leukocytes, mostly eosinophils. Subsequent biopsy specimens showed either more or less obvious subepidermal detachments or little isolated intra- or subcorneal spaces filled with mononuclear cells and polymorphs, together with a dense infiltrate of eosinophils in the dermis and microabscesses in the papillae.

Case 2.—A woman aged 20 who had had repeated attacks of herpetiform Duhring's disease with occasional lesions in the mouth. The first biopsy specimen showed the presence of a subepidermal bulla of medium size, containing very few cells, also a superficial bulla of similar volume situated between a greatly reduced granular layer and a parakeratotic horny layer and containing only a few polymorphs. Between the two blisters, the epidermis was intact. A second biopsy showed a voluminous intracorneal bulla surrounded by parakeratotic lamellae containing serum and numerous neutrophil polymorphs. Under the epidermis, particularly below the bulla, serum and fibrinoid deposits were to be seen with dermal necrosis and groups of pyknotic polymorphs at the level of an early dermo-epidermal separation.

Case 3.—A woman aged 33 presenting with a disseminate eruption of the herpetiform variety of Duhring's disease, itchy and recurrent but very favourably influenced by sulphapyridine. The histological preparation showed three superficial spaces lying between a thin granular layer and a parakeratotic horny layer. The smallest was almost exclusively filled with mononuclear cells and polymorphs. The epidermis showed neither oedema nor cellular infiltration. Beneath it but in contact with basal cells or even necrotic cells of the deeper malpighian layers there were numerous foci of pyknotic polymorphs and fibrin with traces of dermo-epidermal splits.

Group II: This comprised two cases of clinical Duhring's disease in which the intraepidermal bullae were not accompanied by subepidermal detachments.

Case 4.—A man aged 45 with extensive Duhring's disease of herpetiform type. In the biopsy specimen, an isolated blister was removed from skin that was otherwise clinically normal. It showed a bulla immediately below the granular layer, separating it from a normal horny layer. It markedly compressed the rete which was the site of a moderate cellular infiltration. The superficial dermis was fairly oedematous and contained polymorphs, mostly eosinophils. The bulla was full of fluid with some polymorphs, most of which were eosinophils. A second and smaller bulla was removed from the edge of an erythematous patch. This was even more superficial, lying subcorneally on the point of eviction. It contained fluid and polymorphs, some of which were pyknotic. The epidermis was spongiotic, the dermal papillae beneath it containing accumulations of polymorphs undergoing pyknosis in the middle of a patch of oedema.

Case 5.—A woman aged 35 with an itchy eruption present for three years, with bullae large and small in the manner of Duhring's disease. In a biopsy specimen there was a voluminous superficial bulla which was almost multilocular, one half of it situated almost immediately beneath a normal horny layer and the other half reaching more deeply between the cells of the upper malpighian layer which were partly necrotic or ballooned and separated by the accumulation of fluid and cellular infiltration. The subadjacent dermal papillae were oedematous and there were numerous foci of epidermal necrosis, fibrinous deposits and collections of polymorphs, some pyknotic.

Group III: Here we placed five cases in which the diagnosis of Duhring's disease could not be formally asserted and in which the histological picture consisted almost entirely of subcorneal bullae. In these cases in three women and two men, the diagnosis of Duhring's disease seemed very probable. The histological examinations showed sub- or intracorneal bullae of greater or lesser dimensions. At times they were multiple in the same preparation and the abundance of their content of serum and cells (polymorphs, eosinophils, malpighian and parakeratotic cells) respectively seemed to depend on the age of the blister. The rete was generally intact with the exception that at times there were necrotic malpighian cells in contact with the blister or discrete foci of spongiosis. The dermal papillae were a little oedematous with more or less numerous polynuclear cells, often eosinophils, sometimes pyknotic but without a trace of dermo-epidermal splitting. In one of these cases, the lesions consisted of intracorneal foci of parakeratotic cells steeped in coagulated serum and might be interpreted as desiccated bullae about to be thrown off.

DISCUSSION.

In all of these cases, even if superficial bullae coexisted with subepidermal, there was no connection between them, as was shown by examining closely adjacent sections. It was certain that the apparently intraepidermal bullae were not diverticulae of subepidermal blisters. Further, in our cases at least,

it could not be considered that the superficial bullae were initially subepidermal and had ascended the epidermis with its regeneration. We have never in fact seen intraepidermal clefts intermediate in position between the extremes.

We believe that the most plausible explanation of the formation of subcorneal bullae is the exudation of fluid and cells through the epidermis. The migration of serum and cells which come to lie under a resistant, impermeable horny layer would be favoured by necrosis of the deep layers of the epidermis even if limited by the area of contact with the subadjacent lesions in the dermal papillae. This hypothesis would lend important significance to the lesions described by Piérard, Dupont and Fontaine in the herpetiform type of Duhring's disease, not only in the realm of diagnosis but also physiopathologically in the explanation of the formation of superficial bullae. This mechanism would not exclude the formation of cavities high in the rete through the necrosis of cells of the superficial layers of the epidermis. But this event, which has been noted by various authors, seems to us to be much rarer and the superficial necroses which are sometimes seen appear to us to be mainly secondary.

These histological atypicalities do not place in doubt the distinction between Duhring-Brocq's disease and the pemphigus group, for here the acantholytic phenomena are too contingent and manifestly do not correspond to the mechanism of formation of the bullae of Duhring's disease. On the other hand, epidermal necrosis cannot be retained as the fundamental criterion of bullous erythema multiforme, excluding a diagnosis of Duhring's disease. Besides, when this epidermal necrosis is present in Duhring's disease, it is generally much more limited and seems to correspond in the deep layers to an initial lesion and in the superficial to a process of extension of pre-existent cleavage.

The forms with purely subcorneal bullae pose the problems of their integration in the category of Duhring-Brocq's disease and of the identity of the subcorneal pustular dermatosis of Sneddon and Wilkinson (1957). One might in fact object that certain cases with subcorneal blisters or pustules and labelled Duhring's disease belong to the category of Sneddon and Wilkinson's pustulosis, or on the contrary that the latter is nothing more than a variety of dermatitis herpetiformis. Duhring (1884) himself described a pustular form and recently Reynaers (1958) in describing a case affirmed the identity of the two affections.

We think however that despite the anatomical resemblances which are sometimes close, it is correct to accept Sneddon and Wilkinson's pustulosis as a separate entity because the content of the subcorneal pustules is much more cellular than serous and the subadjacent dermo-epidermal changes evocative of dermatitis herpetiformis are lacking. The same argument arises *à propos* the generalized forms of pustular bacterid of Andrews which Hellier (1956) has compared with Sneddon and Wilkinson's pustulosis but which might be identified as a pustular form of Duhring's disease.

The cases which we report seem to us to belong to the group of Duhring's

disease, whether they showed both subcorneal and subepidermal bullae or the former alone. Most of these cases were clinically herpetiform, but pemphigoid forms were not excluded.

CONCLUSION.

A subepidermal bulla does not seem to be the exclusive histological criterion of Duhring-Brocq's disease and the occurrence of a superficial intraepidermal split does not appear to constitute an objection to the diagnosis. In our experience, subcorneal bullae are not exceptional.

Whilst these superficial bullae and likewise the dermo-epidermal lesions described by Piérard, Dupont and Fontaine are features of the herpetiform variety particularly, we believe in the unity of Duhring-Brocq's disease.

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ERYTHEMA NEONATORUM ALLERGICUM.*

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Paris.

It seemed of interest to reinvestigate a neonatal dermatosis whose frequent occurrence contrasts with the indifference which dermatologists display towards it. In doing so, we render homage to our London colleagues, for was it not here, in 1752, that our predecessor Smellie described an erythema of the newborn with a benign course and clinical description resembling that of the disease with which we are dealing? Later we encounter the names of Steiner (erythema papulatum), Leiner (erythema toxicum) and above all Mayerhofer, who published an important paper in 1927 entitled "erythema allergicum". In 1957, Taylor and Bondurant of Ann Arbor found in neonates the considerable incidence of 31%.

Our personal observations concern 42 cases seen in four months amongst 400 newborn babies, i.e. about 10%. The eruption makes its first appearance at a very early age: 29 cases appeared within the first twenty-four hours of life, one at the sixth hour. It generally lasts for two days and never more than six. The eruption is the sole symptom: let us say once and for all that it does not seem to upset the infants and that it is unaccompanied by any disturbance of general health. It is ubiquitous and spares neither the face nor scalp: however it has three sites of election, viz. the back, the front of the chest and the thighs. The eruption is composed of discrete disseminated elements and is of two types:

(i) erythemato-papular type—red or pink patches 10 to 40 mm. in diameter with very irregular contours like those of a map, disappearing with the pressure of a glass slide and centred on lenticular, papular elevations which are distinctly palpable.

(ii) pustular type—the erythematous patches are smaller and in particular they are centred on white protuberant and slightly acuminate pustules. If these are opened with a needle, a fairly abundant quantity of white fluid escapes. After several successive waves, the rash disappears completely in two to six days and does not leave pigmented macules.

Are the patients with this disorder peculiar in any way? We have been unable to find any aetiological factor. The sexes are involved equally: there is no racial or familial preponderance. A family history of allergy is not unusually frequent. No blood group is predominant. With regard to the children themselves, we have been struck by three particular features: they are almost always over 3 Kg. (6 lb. 10 oz.) in weight, they have abundant lanugo hair and desquamate freely.

Investigations.—The most important fact is that the purulent fluid is sterile in contrast with the highly septic nature of pemphigus neonatorum and impetigos. Further, it never contains less than 50% of eosinophils and up to 95% may be present at times. This eosinophilia is not an isolated event for it goes hand in hand with a blood eosinophilia of more than 7% in half the cases and this reaches 15% in the pustular form. Histologically, the greatest difficulties are encountered, which will not surprise anybody who has studied the dysidroses or sudamina, for it seldom happens that the plane of section is fortunate, the follicular and sweat duct orifices

* Paper read at the Franco-British Reunion held in London on 8 July 1960. Dr. Duperrat's address is 176 Bd. St.-Germain, Paris VI.

always being more or less oblique relative to the surface of the skin. So much so that it is difficult or even impossible in many instances to say if one is dealing with a folliculitis or an eccrine poritis. We have the impression that both exist at one and the same time. In every case the essential lesion is a round subcorneal vesicopustule (Figs. 1 and 2), perfectly delimited at first and composed of a very dense mass of polymorphs. These last are both neutrophil and eosinophil with a heavy preponderance of the latter amounting to 70-95%. These polymorphs are never lysed or pyknotic and never show phagocytosed bacteria. The erythematous zones merely show a layer of oedema distending the papillary body, dotted with intact polymorphs.



FIG. 1.—Photomicrograph of the central papule in the erythematopapular form. The ostium is filled with a collection of polymorphs, mainly eosinophil.

What is the nature of this eruption? One's first reaction is to blame infection, but there is none: no positive culture has ever been grown from the pustules, throats or blood of the patients. Animal inoculations are fruitless. Besides, the malady is not in the least contagious and never leads to complications.

Mayerhofer, who made the most extensive study of this subject, incriminated an allergic mechanism, chiefly because of the high eosinophilia of the vesicle fluid and blood. But what is the allergen? Nobody has been able to say. We made tests with bilirubin, milk and maternal vaginal secretions. All were negative (and two of the children were born by caesarean section). Are we

then to invoke hypersensitivity to bedding, air, water or light? We do not know. But we must point out that when these patients are undressed in full daylight, the eruptive elements become more apparent and more numerous in one case in three. On the other hand, ultra-violet and infra-red rays do not

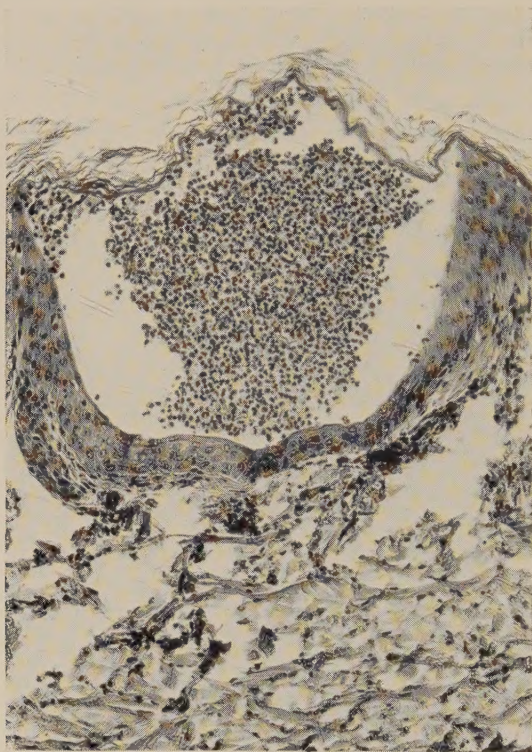


FIG. 2.—Photomicrograph of a protuberant pustule. The roof is formed by a thin horny layer.

modify the eruption at all. Finally, we have been unable to attribute the disorder to drug reactions in the mothers.

CONCLUSION.

The so-called "allergic" erythema of the newborn seems to occupy a place apart in the still confused group of sudamina and miliaria. An anecdote demonstrates its practical importance. Our colleague Dr. Dubois was called to a maternity clinic to see a baby two days old who was covered with pustules. The obstetrician was very upset because he was certain that staphylococcal infection was involved and he envisaged the immediate closure of the clinic. Dubois, who had followed all our cases, recognized erythema neonatorum allergicum at a glance and predicted a prompt cure without treatment of any kind. Two days later, the amazed and incredulous obstetrician had to accept the evidence.

THE VISCERAL LESIONS OF KAPOSI'S DISEASE.*

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THE autopsy of a case of Kaposi's disease suggested to us that it would be of interest to review our knowledge of its visceral localization. As we do not set out to defend any attitude towards its histogenesis, from which the various names of this disease are derived, we shall not employ the term sarcoma or sarcomatosis, not yet angiomatosis, angioreticulosis (Dupont) angiogenic reticulosis (Margarot, Rimbaud and Cazal) or angiofibroblastic reticulosis (Sézary). We shall merely use the vague term Kaposi's disease which seems to suffice.

THE FREQUENCY OF VISCERAL LESIONS.

In 1872, Kaposi wrote that at a given moment in the evolution of the cases he had studied there supervened fever, bloody diarrhoea, haemoptysis, marasmus and death: at autopsy a large number of haemorrhagic tumours comparable with those in the skin were found in the lungs, liver, kidney, heart, small intestine and descending colon.

Since then, most authors have conceded that deep localization was relatively rare and encountered in only 10% of cases—there having been some 60 autopsies in the 600 published (Tedeschi, 1958). Nevertheless, Cox and Helwig (1959) reported extracutaneous foci in 12 out of 14 autopsies. Is this discrepancy in the appreciation of the frequency of visceral lesions fortuitous or does it depend on the fact that autopsies are rarely performed? We cannot say. However, if one adds to the true visceral lesions of Kaposi's disease those which are not specific but merely reactive, it can be said that the internal organs are far from spared.

THE SIMILARITY OF THE CUTANEOUS AND VISCERAL LESIONS.

All authors agree that the visceral lesions show microscopical changes completely similar to those in the skin, a fact which we need not stress. However, haemosiderin deposits and lymphocytic infiltrates are more marked in the visceral lesions than in those of the skin (Cox and Helwig). Allowing for the fact that these deep lesions are more often found at autopsy than during surgical exploration, they present less varied appearances than those of the skin. They are more stereotyped and of a late stage, i.e. "hyperplastic", to

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adopt the classification approved by Dorffel, Montgomery and Lever. As far as we know, early lesions of the granulomatous type have not yet been encountered.

THE PRINCIPAL VISCERAL LESIONS.

Before going into detail about the visceral foci which are most often found in patients with skin lesions, it is necessary to lay emphasis on some relatively recent ideas concerning the existence of deep lesions either in isolation without cutaneous ones, or which precede the appearance of the latter. In principle, no organ is spared since all contain primitive mesenchymal cells which are undifferentiated and capable of giving rise to the "tumours" of Kaposi's disease.

The gastro-intestinal tract from mouth to rectum is predominantly involved. In 50% of cases it is the site of lesions usually in the form of nodules spreading from the submucosa into the mucosa, which may ulcerate, giving rise to haemorrhage. Clinically, digestive symptoms are commonest. Gastric pain, sometimes preceded by haematemesis, diarrhoea or, on the contrary, signs of obstruction even to the point of intussusception (Tedeschi) or fatal occlusion have been witnessed, with or without intestinal bleeding.

Interesting radiological studies have been made. The lesions present the appearance of polyps (Stats, 1946). A comparable picture has been seen by our friend and colleague J. Bonnet of Marseilles, the gastric mucosa showing normal folds from which projected clear little areas arranged like a string of beads. A very different picture is that of a large intra-abdominal air pocket, visible radiographically, formed by the extension of the disease from the mesentery into a loop of bowel (Sherwin and Gordimer, 1952). In one of our recent cases, a complete radiological examination of the gastrointestinal tract was negative.

Pathologically, angiomatous nodules are frequent in the stomach and even more frequently in the small intestine. They are rare proximal to the cardia. In the stomach, the mucosa overlying the nodule is usually intact. In the intestine, on the contrary, the mucosa is penetrated by nodules which cause dark red swellings, sometimes ulcerated. The musculosa is spared: accordingly, intestinal perforation has not been reported. In this location, as in the skin, spontaneous regression may be witnessed. It is, however, impossible to say when the intestinal nodules start, as the signs which they evoke occur late in the disease and herald the approach of death (Favre and Josserand, 1936). Nodules may also occur in the colon, but they are rare.

In one case we noticed angiomatous nodules in the small intestine surrounded by ecchymotic or hypervascularized zones as large as lentils, hard, palpable and occupying the whole thickness of the wall, sometimes projecting into the lumen of the gut or from its surface. Microscopically, under the submucosa

there was extensive infiltration with tumour tissue completely identical to that of the skin—richly cellular foci of fusiform elements in the centre of which angiomatous tissue often lacunar in appearance was developing. Deposits of haemosiderin staining with the Perl's technique were relatively abundant.

Next in order of frequency is involvement of the respiratory system, principally the lungs and pleura. They are rarely visible radiologically. Numerous lesions occur mainly around the vessels and bronchioles and even under the pleura. Intravascular formations compatible with metastatic emboli have been reported (Cox and Helwig).

The disease may also localize in the superficial or deep lymph glands, where, as in other solid organs, it can be seen that the lesion originates in the perivascular tissue, extending into the parenchyma.

Although Kaposi described them, lesions of the heart and pericardium do not often seem to have been recognized in the past. Recently they have been reported as frequent (Tedeschi *et al.* 1947). In addition to involvement of the myo- and pericardium, vascular obstruction has been observed (Cox and Helwig).

The liver may also be the site of tumours which are usually detected *post mortem*. In 1960, Dupont and Sonnet (personal communication) detected a hepatic lesion in a Leopoldville negro by needle biopsy. Renal involvement was detected by the same means.

Besides the involvement of bone and bone marrow, to which we shall return, other organs have been less frequently the sites of deep lesions of Kaposi's disease. The spleen (Paolini, 1927; Symmers, 1941) kidney (Nesbitt *et al.* 1945) pancreas (Cox and Helwig, 1959) thyroid (Nesbitt *et al.*, 1945) testes (Rossi, 1928) seminal vesicle and suprarenal gland (Cox and Helwig, 1959) and even the brain (Nesbitt *et al.*, 1945).

Whilst as we have already said, and as the foregoing enumeration shows, no organ is spared by the disease, autopsy reports are rare in which there are details of multiple deep disseminated foci resembling metastases. An exception is the report of a case by Nesbitt *et al.* who described involvement of the gastrointestinal tract, heart, lungs, liver, spleen, lymph glands, several vertebrae, thyroid and brain—but cutaneous lesions were absent.

Besides these specific deep lesions with angiomatous nodules, there often seems to exist an involvement of the lymph glands and viscera characterized by hyperplasia which is apparently non-specific, purely reactive and inflammatory in appearance, involving organs rich in reticuloendothelial tissue. These reactive hyperplasias precede or accompany the evolution of the disease to such a point that it may be asked whether they do not constitute precocious manifestations which end as lesions of Kaposi's disease, which one knows are not always static. Thus a certain number of examples of lymphadenopathy and particularly of splenomegaly have been observed. Greppi and Bettoni (1932)

reported a hyperhaemolytic spleen showing sinus hyperplasia. Uregli (cited by Olmer *et al.*, 1952) examined a spleen weighing 1340 g. in which he was unable to detect anything more than a great abundance of macrophagic histiocytes. The spleen of a patient of Stats (1946) weighed 700 g. but histologically showed only reticular hyperplasia. In the case of Tedeschi *et al.*, the spleen weighed 250 g. and showed marked sinus hyperplasia. A patient of Olmer *et al.* showed typical Kaposi's disease and a very large spleen: at autopsy it weighed 1200 g. Microscopically, the authors found fibrosis of the spleen associated with reticulo-endothelial lesions and hyperplasia of the Kupffer cells in the liver, which weighed 2000 g. In our case the spleen showed a very thickened capsule with hyperplasia of the red pulp compared with the white, and a particularly massive infiltration with pigment. The deposits of haemosiderin involved the endothelium of the venous sinuses and the reticulum cells of the cords of Billoth. This deposit was also extracellular, lying *en bloc* in the connective tissue septa and particularly in the capsule in which it formed a veritable carapace. The hyperhaemolytic activity of the spleen had therefore reached a remarkable degree. To be complete it must be added that a fine hyalinization of the splenic vessels was observed.

The bone marrow may also show a hyperplastic state characterized principally by an increase in reticulum cells and the cells of the monocyte series. Such "reactive" states may explain certain anomalies of the blood picture sometimes observed in Kaposi's disease. It is known that lymphocytosis of the blood has fairly frequently been found and even an abundance of atypical mononuclear cells midway in type between lymphocytes and monocytes. In 1932, Flarer reported a case of Kaposi's disease with haematological changes involving mononuclear cells which Bertaccini (1942) considered unclassifiable. Dupont attaches great importance to these qualitative and quantitative differences in the leukocytes in Kaposi's disease. It is particularly tempting to interpret these blood anomalies as the result of reactive hyperplasia of the reticulo-endothelial system whose elements are known to give rise to the stem cells of the lymphocyte and monocyte series. On the other hand, the red cell count is usually fairly normal. To other authors these anomalies of blood monocytes are banal, comparable with those frequently encountered in chronic disease, such as tuberculosis.

THE ROLE OF THE VISCERAL LESIONS IN THE FATAL OUTCOME.

The duration and evolution of Kaposi's disease is extremely variable. According to Kaposi himself it could be two to three years. Later he estimated ten to fifteen. Kren observed a patient who lived forty-six years after the first lesions manifested themselves. If the cure of the disease does not seem to have been witnessed, the disappearance of certain lesions is a well established event. Certain authors even report that among the nineteen survivors of forty-four

patients with the disorder whom they had observed for a long time, ten no longer showed a trace of the disease (Cox and Helwig). Just as the regression of cutaneous lesions has been established, so has the healing of certain deep foci, as is shown particularly by "cicatrized" cardiac lesions (Tedeschi). This regression is produced as the consequence of the progressive proliferation and invasion of fibrous tissue as is the case in most granulomas. Such regression fits the argument of those authors who see the disease more as a hyperplasia than a neoplasia and therefore one incapable of giving rise to metastases.

From the point of view of prognosis, it is undeniable that concomitant involvement of the viscera is of very grave significance. But it is curious to note that of the twenty-five fatal cases of Cox and Helwig, death occurred in only eleven cases as the result of Kaposi's disease, whilst in ten it was due to independent causes and in four the cause of death was unknown or unestablished.

ISOLATED VISCERAL LESIONS.

Up to the time of Dorfelf's work, Kaposi's disease was considered to be predominantly a disease of the skin and subcutaneous connective tissue capable of giving rise secondarily to deep visceral foci late in the illness. We shall see that this old conception of the metastatic origin of visceral involvement is no longer unanimously admitted. Furthermore as we have already said, several papers have been published concerning visceral lesions which appeared before cutaneous involvement (Paolini, 1927; Pearce and Walker, 1936) and even without skin lesions at any stage. The recognition of these visceral localizations, primary or isolated, was naturally made possible by their close histological resemblance to those of the skin. In this way, several cases of visceral Kaposi's disease without cutaneous involvement have become known, mainly with foci in the heart, kidneys, digestive and respiratory tracts (Choisser and Ramsey, 1939; Cox and Helwig, 1959; Nesbitt *et al.*, 1945; Tedeschi, 1958). These visceral lesions have aroused the scepticism of some authors regarding their metastatic origin. They tend to view Kaposi's disease as a systemic disorder whose foci can appear anywhere, in the skin or viscera independent of one another, i.e. multicentrically. In most of these cases, these lesions, both cutaneous and deep, have a histological picture which is characteristic, with an intimate mixture and association of fusiform cells and hyperaemic vascular spaces. They neither degenerate nor metastasize, but in a small number of cases, malignant transformation may arise in one or several of the cutaneous or deep foci, giving rise to an angiosarcoma or an undifferentiated sarcoma seen at times within or alongside typical lesions showing no degeneration. It is in the course of this inconstant phase of malignancy that Kaposi's disease may, like any other cancer, give rise to metastases, as is shown by the occurrence of emboli in the pulmonary blood vessels (Cox and Helwig).

THE ASSOCIATION OF KAPOSI'S DISEASE WITH OTHER NEOPLASMS.

Observation of the association of Kaposi's disease and malignant degenerative processes is not exceptional. One might, it is true, regard these as fortuitous or occasional when they involve an epithelioma. We are greatly obliged to Dr. Jadassohn and Dr. Musso of Geneva for a personal communication regarding two examples of this type. In the first, a carcinoma of the oesophagus and a fungating cancer of the caecum were demonstrated in a patient with Kaposi's disease of the skin: in the second, two years after the diagnosis of cutaneous Kaposi's disease, an ileo-caecal neoplasm was discovered and hepatic metastases demonstrated by needle biopsy. Our own case had for some months before death suffered from oesophageal dysphagia whose cancerous origin was suspected radiologically. A palliative gastrostomy was attempted. At autopsy, a squamous-cell carcinoma of the oesophagus was easily confirmed, together with metastases in the lymph glands.

The other malignant associations of Kaposi's disease are more interesting, for they open the door to discussion of a common histopathogenesis. They are encountered with relative frequency. Association with myeloid leukaemia (Fischer and Cohen, 1951) seems less frequent than with lymphoid (Cole and Crump, 1920; Cox and Helwig, 1959; Hufnagel and Dupont, 1931; Sachs and Gray, 1945; Van Cleve and Hellwig, 1935). Della Favera (1911) observed two cases with white cell counts of 26,320 and 37,000 respectively. One might also consider the blood anomalies already cited, involving an abundance of mononuclear cells, not only as hyperplastic reactions but also as states bordering between leukocytosis and leukaemia. Even more arresting are the associations between Kaposi's disease and Hodgkin's disease (Cox and Helwig 1959; Greenstein and Conston, 1949; MacCarthy and Pack, 1950; Osborne *et al.*, 1947) and with mycosis fungoides (Cox and Helwig, 1959; Lane and Greenwood, 1933; Winer, 1947), Brill-Symmers disease (MacCarthy and Pack, 1950) and lymphoblastoma (Epstein, 1957; MacKee and Cipollaro, 1936). Such disorders are of course considered to be anarchic neoplastic hyperplasias of the reticulo-endothelial system. For certain authors, however, these apparently frequent associations are not enough to make Kaposi's disease a disease of the reticuloendothelial system.

We must also cite a syndrome recently isolated by Stewart and Treves (1948)—lymphangiosarcoma in cases of lymphoedema after mastectomy—whose metastases closely resemble those of Kaposi's disease. According to Treves, this similarity is only encountered in the late stage.*

The involvement of viscera seems to indicate that Kaposi's disease is not a purely cutaneous malady. Also, given their prognostic importance, the ob-

* We are greatly indebted to Dr. J. Civatte of Paris for histological preparations of post-mastectomy lymphangiosarcoma as well as slides of Kaposi's disease associated with Hodgkin's disease.

servation of each case necessitates systematic and periodic investigation for deep lesions—radiological examination of the chest, gastrointestinal tract and heart, electrocardiograms, needle biopsy of viscera, especially the liver, and examinations of the blood and stool.

An attempt at surgical removal when it is technically possible or a trial of deep therapy with radiocobalt may be suitable in certain cases of visceral localization which considerably darkens the prognosis of the malady.

CONCLUSIONS AND RESUME.

Perhaps less rarely than is classically taught, visceral localization of Kaposi's disease appears to constitute a not inconsiderable aspect of the clinical course and pathological anatomy of this disease.

Such foci may take the form not only of specific lesions but also of a non-specific reactive hyperplasia of the reticulo-endothelial system.

Whilst they are generally encountered in patients with cutaneous tumours, they may also be seen in isolation without cutaneous involvement.

Just like the cutaneous lesions, these visceral foci may degenerate on their own account and in a small number of cases give rise to metastases.

Finally, it is not exceptional to see associations between the lesions of Kaposi's disease and malignant conditions in which the point of departure is often a degeneration of the reticuloendothelial system.

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URINARY SUBSTANCES PROVOKING ALLERGIC REACTIONS.*

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WE are indebted to Barber and Oriel (1928) for an original hypothesis, viz. that during allergic attacks, biologically active nitrogenous substances (which Oriel believed to be proteoses) are excreted in the urine. They also suggested the possibility of the therapeutic use of the allergen isolated in this way—imperfectly it is true—in desensitization.

Those who attempted to verify these ideas fell into two irreconcilable clans. The majority, particularly the English speaking authors, rejected the whole hypothesis and its therapeutic rider (no man is a prophet in his own country). A small number, myself included, obtained results which were consonant with the ideas of Oriel and Barber, even if they failed to confirm them in every particular, especially where skin tests were concerned. Later on, Barber came to the conclusion that his hypothesis was of uncertain value and he disowned his brain child.

Since that time, I have modified the technique of extraction. Oriel's "substance P" was not a proteose. The methods by which the undetermined active agent was obtained resulted in the production of an inert precipitate which adsorbed the biologically active substance. This method was recommended by Urbach and Gottlieb (1946) in their classical book. On the other hand—and I confess that I have no blind faith in skin tests—I was particularly impressed by indubitable therapeutic successes and focal reactions which were often of extraordinary intensity.

I had the idea, which was of no practical consequence, that the adsorbent precipitate was urinary mucus. We are now more familiar with urinary mucoproteins. I resumed my former researches and present my first incomplete and imperfect results in homage to Barber and Oriel, the misunderstood founders of urinary allergology.

The method, which may be open to improvement but which I favour at present, is as follows.

(i) *First Stage. Concentration of urine.*—A drop of chloroform is added to the urine passed during an attack. It is then placed in a cellophane tube suspended vertically in front of a fan: a convenient tube is the sort which is used in the manufacture of certain sausages. In 24 hours a litre is reduced to 50–100 ml. The hypertonicity resulting from the evaporation prevents the growth of micro-organisms: a urine containing numerous coliforms shows next day only dead bacilli, structurally unchanged. This diminution in volume is achieved without any alteration of biological

* Read at the Fourth Franco-British Reunion in London, 1960.

properties, as there is no change in temperature or addition of chemicals (the chloroform can be ignored).

(ii) *Second Stage. Precipitation with alcohol and acetone, with or without previous dialysis.*—One volume of concentrated urine treated with five volumes of a mixture of equal parts of 95% ethyl alcohol and pure acetone gives the active precipitate. Sometimes I use the whole concentrated urine without removing the mineral precipitate resulting from the concentration of the original urine. At other times I dialyse the concentrated urine against double distilled water to which a little chloroform has been added and which is of neutral pH. Here the addition of chloroform is indispensable to avoid any bacterial contamination. An excellent arrangement is the following. The cellophane tube containing the urine is plunged into a beaker so that the levels of the liquid to be dialysed and that of the water are on the same horizontal level: a piece of cardboard with a central perforation prevents contamination with dust. The whole stands in front of a fan. In this way an increase in the volume of the undialysable liquid is prevented.

After being left for twelve hours at 4° C., the precipitate looks different according to whether the urine has been dialysed or not, probably because of the different concentrations of electrolytes. In the non-dialysed urine, the precipitate is voluminous with a clear supernatant. In the dialysed urine it forms a large coherent clot which falls rapidly to the bottom of the vessel: it has an opalescent supernatant which at 4° C. flocculates in turn after 24 hours.

(iii) *Preparation of solution.*—The centrifuged precipitate, dried as quickly as possible (one hour at 37° C.), is suspended in physiological saline containing a little chloroform and of neutral pH. In a completely arbitrary fashion, but one which avoids any dessication which would harm the biological properties, I use 30 ml. of physiological saline for an initial volume of urine between 500 and 1000 ml. and 15 ml. for a smaller volume. I carry out skin tests to gain an idea of what dilution to use therapeutically.

The empirical nature of this method and its theoretical shortcomings are evident. The cause of all these gropings is the impossibility of resolving the problem which was posed by "substance P" and which has remained unanswered. If it is now quite certain that the chemical substrate of the flocculate is the sum total of the urinary mucoproteins, two theoretical possibilities emerge.

(i) During pathological states, an abnormal mucoprotein appears: it has new and harmful biological properties in the same way as the substrate of antibody function is composed of globulins which are modified and different from physiological globulins.

(ii) During a pathological state, an undetermined noxa is excreted which is adsorbed on to the urinary mucoproteins. The morbid properties we have studied are ascribable to it and not to the mucoproteins which adsorb it and which are all that we can isolate. A method of elution remains to be discovered.

Isolated by this method, the precipitate which is obtained from the urine of a healthy individual has the following experimental properties.

(i) It is a hapten. It does not produce anaphylaxis in the rabbit or guinea-pig and it does not cause shock in a rabbit or guinea-pig prepared with oval-

bumin. By intravenous route it produces fatal anaphylactic shock in a rabbit prepared by the intraperitoneal introduction of human tissue.

(ii) It can be used to produce the Sanarelli-Shwartzman phenomenon in the rabbit.

On the other hand, the precipitate obtained from an abnormal urine, whether dialysed or not, and employed in the patient who produced it, often gives rise to focal reactions such as I have described with "substance P". It also gives rise to immediate or delayed cutaneous reactions which remain difficult to interpret. I consider the problem unresolved. There appear to exist in "normal" urines some substances capable of provoking positive reactions in certain cases and in particular I am partisan to the hypothesis of urinary histamine liberators, perhaps related to urochrome. It is apparent that we encounter the same difficulties as those raised by Oriel's substance, but the therapeutic results allow us to approach them in a constructive spirit.

Since I perfected the technique of extraction which I have just explained, I have obtained interesting therapeutic results in three categories of dermatological indication.

(i) As I have remarked elsewhere, it appears that the treatment prevents relapses of recurrent erythema multiforme even though it does not perceptibly influence the attack present when the treatment is started.

(ii) Recurrent aphthous ulcers, with their incessant attacks, capricious and painful over months or years, are influenced remarkably. The eruptive elements on the mucosa ulcerate less deeply, the pain diminishes to the point where eating becomes possible and the attacks are less frequent with intervals of freedom which become progressively longer. It seems as though the inoculations lose their effect and it is necessary to continue treatment with a new extract obtained during an attenuated attack. In these conditions one obtains final and veritable cures or such ameliorations that the patients are satisfied.

(iii) Two adult patients with dermatomyositis have derived great benefit from the treatment. The lives of both were indubitably saved by corticosteroid therapy and then their condition remained stationary thanks to an alcoholic solution of tocopherol quinone which I employ in such cases. The treatment seems to have cured one of the cases after having produced subcutaneous nodules at a distance from the sites of injection. The second is so improved that complete cure can be anticipated. I cite these cases with much hesitation but the hopes which they arouse justify their being mentioned.

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FOLLICULAR MUCINOSIS*.

(ALOPECIA MUCINOSA, PINKUS).

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IN 1926 Kreibich described a case of *erythrodermie en plaque disséminées* which on histological examination revealed a mucinous degeneration of follicles besides the banal changes of the condition. (Figs. 1, 2.) In 1939, Lehner and Szodoray reported a case of patchy dermatosis with similar histological changes and staining properties. The lesion was considered to be of virus origin.

In 1957, Pinkus, unaware of the previous papers, published one dealing with a group of dermatoses characterized by erythrosquamous patches on the face, trunk, extremities and scalp. On the scalp the patches were accompanied by loss of hair. The histological picture common to all cases consisted of mucinous degeneration of hair follicles and sebaceous glands and an inflammatory reaction in the cutis. So Pinkus aptly combined the two salient features of the condition and called it alopecia mucinosa. He considered the condition to be a clinical and pathological entity probably caused by a virus. His paper was followed by similar reports (Braun-Falco, 1957; Jablonska *et al.*, 1959; Johnson *et al.*, 1959; McKenzie, 1960; Martin-Scott, 1958; Stevenson, 1959; Woringer, 1959 and Zackheim, 1958).

I have collected twelve cases of this peculiar condition including the three cases shown by Martin-Scott, Stevenson and McKenzie. They were in ten men and two women, whose ages ranged between 24 and 64. Lupus erythematosus, lymphocytoma, eosinophilic granuloma, mycosis fungoides and ringworm were suggested as possible diagnoses. Only six cases will be considered in this paper.

CASE REPORTS.

Case 1. Dr. Jenner's.

A man of 64. In March 1954 the patient was admitted to hospital, suffering from severe and widespread seborrhoeic dermatitis. This cleared up completely with rest, sedation, simple local applications and a course of protein shock therapy by means of intravenous injections of T.A.B. in increasing doses. He was seen again as an out-patient on 17. x. 56 complaining of multiple scaly patches on the shoulders and back. For one month he had also noticed bald patches on both temples and a patch on the crown. A provisional diagnosis of the premycotic stage of mycosis fungoides or parapsoriasis was made.

* Based on a paper read at the Franco-British Reunion, London, July 1960, and to the Pacific Dermatological Association, September 1960, in Victoria, B.C.



FIG. 1.



FIG. 2.

Investigations. Direct examination of the hairs from the periphery of the bald patch did not reveal any mycelium or spores. No pathogenic fungi were grown on culture. Hb. 97%, W.B.C. 7000/ml. with a normal differential. Red cell morphology on the stained film normal. Plasma proteins 7.2 g.%. Electrophoretic pattern within normal limits. W.R. and Kahn negative. Chest X-ray: slight enlargement of the left ventricle.

Histology. From a lesion on the back. The epidermis showed hyperkeratosis, patchy parakeratosis, acanthosis, focal spongiosis with immigration of round cells,

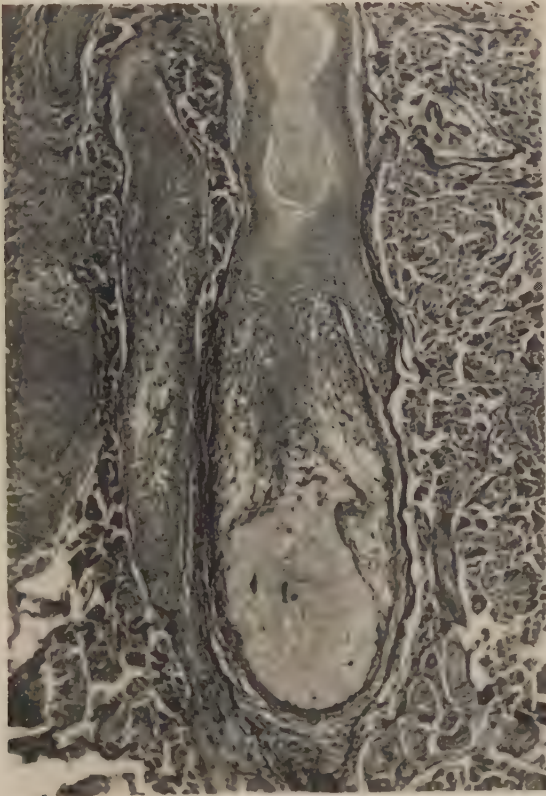


FIG. 3.

The conspicuous feature was a follicle whose walls were widened by intercellular oedema and cyst formation. Both the intercellular oedema and cyst contained aropy precipitate which on staining with conventional stains showed characteristic tinctorial properties. It showed metachromasia with toluidine blue, stained with alcian blue, gave a positive PAS reaction and produced brilliant results with the Hale stain modified by the Rinehart and Abul Haj method (Fig. 3). The staining properties of mucin were removed with testicular hyaluronidase and left unchanged after treatment with diastase. This indicated that the mucin was a mucopolysaccharide. None of my cases showed any involvement of sebaceous glands.

When the patient was re-examined on 12.ii.58 the following findings were noted. At present he has two reddish, slightly scaly patches on both shoulders resembling lichen simplex with increased skin markings. No greasy appearance. No real infil-

tration. There is a similar patch on the neck. The symmetrically disposed patches on the chest and abdomen have completely disappeared. The patch on the scalp is quiescent." When seen on 29.iii.58, it was noted that the hair was regrowing on the upper margin of the patch on the left temple. The patient complained of slight irritation. He was seen regularly at monthly intervals until the beginning of June 1958, since when he has not been seen again.

Case 2. Dr. Bettley's case shown by Dr. Stevenson.

Dr. Stevenson described the history and clinical appearance in the following way : " A woman of 25, who nine years previously, after recovering from erysipelas of the face, developed an itching rash on the forehead, starting on the right eyebrow. She



FIG. 4.

was given x-rays 75 r thrice to the affected areas with temporary benefit. A year later the condition had progressed to involve the left cheek and right nostril : a new lesion also appeared over the right posterior axilla. A year ago the tips of the shoulders became affected and itching papules developed on the lateral aspects of the elbows. Similar itching papules appeared on the buttocks during the past six months. Her present and past health has been good." Indurated erythematous plaques with some superficial scaling and excoriation were present over the eyebrows, forehead, the left cheek, around the right nostril (Fig. 4) and on the chin. There was partial alopecia of the eyebrows. The hair follicle ostia were patulous. Similar plaques over the tips of the shoulders and one over the posterior aspect of the left axilla, showed multiple follicular spinous processes. On the elbows and buttocks were a number of excoriated papules.

Histology.—Portion of a lesion on the face showed numerous follicular cysts filled with concentric keratinous masses lying within the corium which was heavily infiltrated with inflammatory cells. Serial sections revealed the "cysts" to communicate with follicular openings, plugged with keratin. (Fig. 5.) No definite histological diagnosis could be offered at the time. When Dr. G. C. Wells suggested that the case might be one of alopecia mucinosa, a second biopsy of an axillary lesion was per-

formed. The histology confirmed Dr. Wells' diagnosis. There was a marked perifollicular infiltration, the follicles showed hyperplasia and their walls exhibited mucinous degeneration. The first section was then reviewed and the follicular cysts revealed several foci of spongiosis in their walls which on staining with alcian blue showed the presence of mucin (Fig. 6).

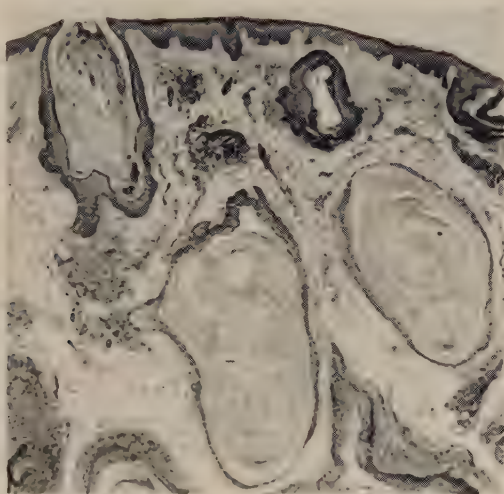


FIG. 5.

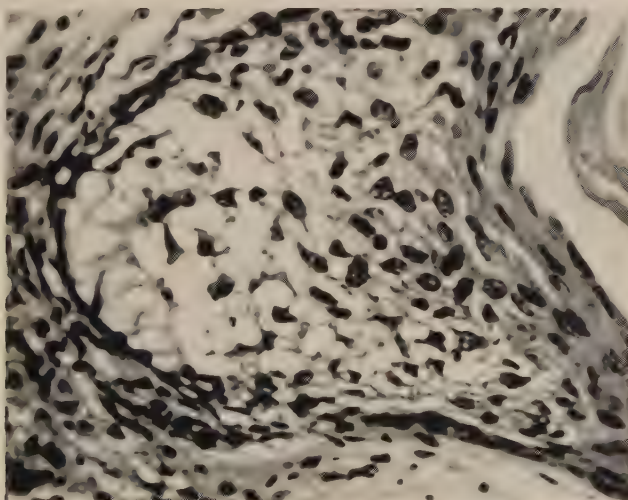


FIG. 6.

Case 3. Dr. Muende's first.

I remembered a case of Dr. Muende's: he was a man of about 60 who showed a peculiar alopecia of both eyebrows with milia and swelling and redness of the skin (Fig. 7). At this time he was diagnosed as a case of ulerythema ophryogenes. I reviewed the slides and found the same histology as seen in the previous case. The epidermis was atrophic. The cutis exhibited several follicular cysts filled with horny

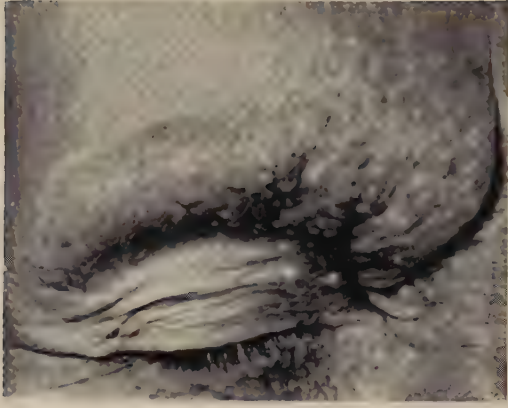


FIG. 7.



FIG. 8.

masses. The walls of some cysts showed intercellular oedema containing mucin. The corium showed fibrotic changes with banal inflammation.

Case 4. Dr. Muende's second.

A man of 59 was seen at the outpatient department with a swelling of the right eyebrow and eyelid for many months. On examination there was marked induration, crusting, scaling and loss of hairs of the eyebrow region and marked oedema with scaling of the upper eyelid (Fig. 8). The clinical picture was unusual and a tentative diagnosis of reticulosis of some sort was suggested.

Histology.—The epidermis showed crusting, hyperkeratosis, parakeratosis, acanthosis with spongiosis and immigration of round cells. The cutis exhibited a very



FIG. 9.

marked dense infiltration consisting of lymphocytes and reticulum cells producing the picture of lymphoreticular tissue (Fig. 9). The follicles were plugged with keratin and their walls showed spongiosis with vesicles containing mucin (Fig. 10). Thus the epidermis showed eczema-like changes, the follicles exhibiting plugging of their ostia and mucinous degeneration of their walls. The infiltration in the cutis suggested localized lymphoma.

Case 5. Dr. Moynahan's case shown by Dr. McKenzie.

This man showed on his right cheek an erythematous elevated patch for several days. Biopsy revealed marked mucinosis of follicles and a mild inflammatory reaction of the cutis. At the time of presentation of the case there was hardly anything to be seen. Squeezing the affected area, however, between two fingers produced a fair amount of mucin, pouring out of follicular ostia. This test was carried out by Kreibich and repeated by Jablonska and is pathognomonic in doubtful cases.

Case 6. Dr. Russell's.

A man of 54 had been suffering from a generalized pruritic eruption for several years. On examination there was a generalized lichenification with enlargement of inguinal glands. The blood count revealed an eosinophilia of 30%. Dr. Russell felt that the case was one of an undetermined reticulosis.

Histology.—The epidermis showed acanthosis and focal spongiosis with immigration of a few round cells. The cutis exhibited perivascular round cell infiltration. Serial sections revealed one follicle surrounded by a marked round cell infiltration. The follicle itself showed marked swelling with cyst formation in the upper and lower parts. The cysts contain disintegrated epidermal cells and mucin.

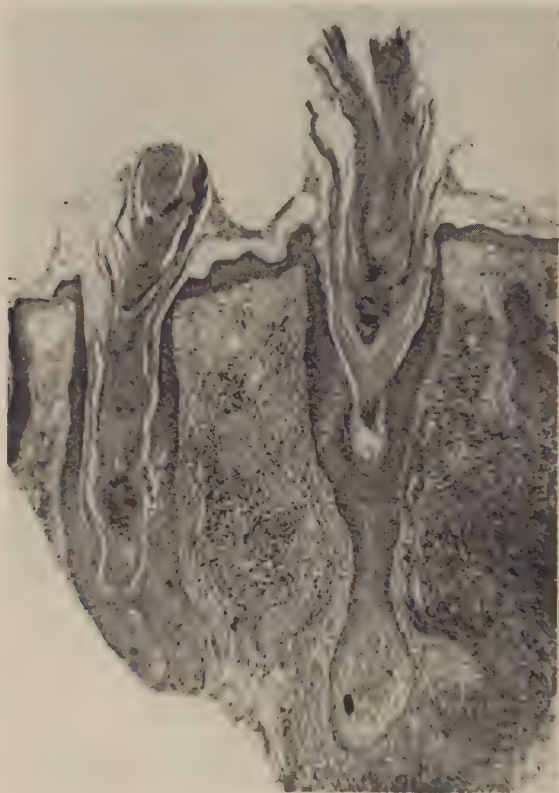


FIG. 10.

DISCUSSION.

It is clear that mucinous degeneration of follicles may be seen in a large group of apparently unrelated dermatoses. One of these cases had a history of seborrhoeic dermatitis (Case 1), whilst another exhibited clinical features indicating neurodermatitis (Case 3). Others suggested histologically a localized lymphoma (Case 4), or possibly a systemic reticulosis (Case 6). One case consisted of a single erythematous lesion without any obvious cause, resolving spontaneously (Case 5). Three of these cases showed conspicuous localization on the eyebrows (Cases 2, 3 and 4).

The histological aspects indicate that follicular mucinosis is not a static process but a dynamic one leading to different histological manifestations. I believe

that the histological appearances I have described represent both ends of this dynamic process. At the beginning there is mucinous degeneration of the follicles. At this stage the condition may clear up without sequelae. If, however, the condition goes on and becomes chronic, then the follicles undergo hyperkeratosis to produce lichen spinulosus clinically ; eventually the follicles may undergo cystic transformation. The epidermis itself may show features of an eczematous histology. The infiltration in the cutis may change according to the nature of the underlying condition.

The aetiology of alopecia mucinosa is unknown. Pinkus suggested originally a virus infection. Jablonska *et al.* regarded the condition as a mucinosis with no evidence of an endocrinological disturbance. Woringer *et al.* regarded the condition as a clinical and histological phenomenon of unknown aetiology. I believe that alopecia mucinosa is a degenerative process occurring only within follicles. I have not observed any changes within sebaceous glands. If they occur, they probably are of a secondary nature, whereby mucin accumulated within the walls of the follicles breaks through into the sebaceous glands. What is the cause of the degeneration ? The virus theory is unsupported by any evidence. Braun-Falco submitted that the mucinosis of follicles was due to mucophanerosis. He stated that mucopolysaccharides were present within the walls of follicles and degeneration of epidermal cells brought the mucin to the fore.

Looking at follicles which show commencing changes of mucinosis, one is struck by the similarity of these changes to those seen in eczema. In follicular mucinosis, there is spongiosis which leads to vesicle formation as in eczema. I have examined several cases of vesicular eczema and found traces of mucin within the vesicles. Without implying that histological similarity indicates similar pathogenesis or aetiology, I am suggesting for the moment that in cases of alopecia mucinosa, or better still, follicular mucinosis, we might be dealing with a hitherto unrecognised phenomenon of eczematous change taking place within hair follicles, leading to the peculiar clinical appearance and thus masking the true underlying nature of the condition. If there is eczema of the nail matrix leading to distortion of nails, why should there not exist eczema of hair follicles ? Many epidermal lesions may continue along the follicles, e.g. pemphigus vulgaris, Hailey-Hailey disease, keratoma, junctional naevi and melanomas.

The clinical picture of follicular mucinosis differs according to the acuteness or chronicity of the condition. Acute eczematous changes within the follicles show clinically as oedematous round plaques, which may disappear without trace, as in McKenzie's case. The more chronic cases show the morphology of lichen spinulosus. The very chronic cases lead to the appearance of milia within the corium, erasing any trace of preceding follicular mucinosis. The last two changes are understandable if one considers that whilst the epidermis gets rid of its secondary inflammatory products by simple exfoliation, this cannot

be so in the case of an eczematous follicle, so that the inflammatory products are partly pushed through the orifices of the follicle in the form of keratin and mucin, leading to the formation of lichen spinulosus. Eventually follicles may undergo cystic transformation.

SUMMARY.

I venture therefore to suggest that alopecia mucinosa is a hitherto unrecognized form of eczema of hair follicles occurring either independently or in the course of chronic dermatoses such as seborrhoeic dermatitis, atopic dermatitis, benign and malignant reticuloses. This leads to spongiosis, vesiculation and then mucophanerosis of the walls of follicles. As in true eczema the changes may be acute, subacute and chronic. Acute follicular mucinosis may lead to erythematous raised patches with temporary loss of hairs. The patch may clear up and hairs will grow again. Subacute cases lead to persistent thickened patches with lesions like lichen spinulosus. Very chronic lesions leave irreparable changes leading to cystic transformation of follicles with permanent loss of hair and milia formation, masking completely the true eczematous nature of the underlying condition.

I wish to thank Dr. F. J. V. Jenner, Dr. F. R. Bettley, Dr. I. Muende, Dr. E. J. Moynahan and Dr. B. F. Russell for allowing me to publish their cases, and to the Springer Verlag for allowing me to reproduce Figs. 1 and 2 from the *Archiv für Dermatologie*, and the Editor of the *Proceedings of the Royal Society of Medicine* for permitting me to use the blocks for Figs. 5, 6 and 7. I am also grateful to Mr. R. Lunnion for the photographs and to Miss M. D. Leuner for secretarial assistance.

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ADDENDUM.

Since completing this paper, I have come across that by Twiston Davies and Ferguson Smith, written in 1943 and entitled "Eczema Epilans: ? a Variety of Dermatitis Atrophicans Maculosa" (*Brit. J. Derm.*, **55**, 39). They described two cases in which patches of chronic eczema healed spontaneously after six to twelve months, leaving permanent baldness in and around the areas affected. Histologically, banal inflammatory changes were noted, with destruction of hair follicles and partial replacement of the collagen by fat. The late Dr. W. F. Freudenthal had examined sections from one of the patients and the relevant block was found at University College Hospital Medical School. I have stained sections from it and succeeded in demonstrating mucin in some of the remaining follicles. Their cases were probably due to alopecia mucinosa and "there is no new thing under the sun".

PRECIPITINS IN THE DIAGNOSIS OF FUNGOUS INFECTIONS.*

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THE demonstration of precipitins in fungous infections has recently provided a renewed interest in serological diagnostic procedures. In discussing work in this field carried out at St. John's Hospital for Diseases of the Skin and Brompton Hospital, London, it would seem appropriate to review briefly the value of immunological studies in mycotic diseases. For this purpose, these infections may be considered in the following four categories.

(i) Systemic mycotic infections involving the lungs and other viscera, and in which skin lesions are not a predominant feature (e.g. coccidioidomycosis and histoplasmosis).

(ii) Localized pulmonary infections in which dissemination of fungus is rare (e.g. aspergillosis).

(iii) Infections in which fungus is restricted to lesions of the skin and subcutaneous tissues (e.g. chromoblastomycosis and maduromycosis). Occasionally such localization may be only apparent, as in some instances of sporotrichosis and North American blastomycosis.

(iv) Mycotic infections of keratin due to *Candida albicans* and ringworm fungi. These are essentially limited to skin and mucosae and only very rarely disseminate.

To exemplify the immunological changes occurring in systemic mycotic diseases, coccidioidomycosis may be cited. This is essentially a benign pulmonary disease and has many similarities to infection by *Myc. tuberculosis*. Infection is often subclinical and only a very small proportion of those acquiring infection develop disseminated disease involving lungs, meninges, skeletal system and skin. *Coccidioides immitis* antigen (coccidioidin) which is used for skin testing and for serological studies is prepared in much the same way as tuberculin. It is standardized on human subjects and shows a minimum of cross reactions. It is mainly polysaccharide in nature and is stable. The limited pneumonitis constituting primary coccidioidomycosis is accompanied by the development of delayed-type skin hypersensitivity to coccidioidin (1 : 100), and in those patients in whom erythema nodosum or erythema multiforme appears, hypersensitivity to 1 : 1000 or 1 : 10,000 coccidioidin may be demonstrable. Subjects exhibiting a positive coccidioidin skin test are considered to be immune to further infection. This sensitivity is lasting and its significance,

* Based on a paper read at the Franco-British Reunion, London, 1960.

therefore, is similar to that of Mantoux reactions. Early in the course of disease, precipitins against coccidioidin become demonstrable in the blood of half of infected patients and are often detectable by the end of the first week of illness. They occur in all but about 10% of patients by the fourth week. The presence of these precipitins is strongly indicative of active infection by *Coccidioides immitis*, and a rising titre is conclusive evidence. On the other hand, precipitins have no prognostic significance. Absence of precipitins does not negate the possibility of infection. Three or four weeks after acquisition of infection, the titre of precipitins falls and this antibody is usually no longer evident after six months. Unlike precipitins, complement-fixing antibodies against coccidioidin are undetectable early in primary disease. Providing dissemination of the causative fungus does not occur, only a low complement-fixing antibody titre develops after many weeks and later this diminishes as infection resolves. As for precipitins, complement-fixing antibodies are highly suggestive of active infection but rising titres are indicative of dissemination of fungus.

Histoplasmin used in the diagnosis of histoplasmosis shows greater cross reactions than coccidioidin and less success has been achieved in attempts to define its active principle. When properly standardized material is used in critical dilutions, however, it is valuable for skin testing. In serological studies it has been found necessary to use not only this antigen but also material prepared from the mycelial and yeast phases of *Histoplasma capsulatum*. Multiple serological tests are of greater diagnostic value than any single procedure. Precipitins and collodion agglutination tests tend to be positive early in disease and for a short period, whereas complement-fixation tests are most often positive in infections lasting longer.

In North American blastomycosis, immunological studies are less conclusive, but similar principles apply. In the form of the disease in which extensive chronic skin lesions manifest themselves, the pulmonary origin of infection may be slight or inapparent radiologically. In such cases an immunological paradox may be present for, in spite of widespread cutaneous involvement, low complement fixing antibody titres are recorded and high skin test reactivity. The possibility that relatively small numbers of *Blastomyces dermatitidis* yeast cells may evoke these cutaneous reactions may explain this paradox. As these immunological observations would suggest, the ultimate prognosis in this syndrome is not unfavourable.

A minimum of success has accompanied the immunological investigation of torulosis (cryptococcosis). Skin testing with fungous antigen, usually employing a suspension of yeast cells, has given little assistance in diagnosis. Antibodies to *Cryptococcus neoformans* have seldom been demonstrated in patients known to be infected, though some success has been achieved with precipitin and complement fixation tests using specific hyperimmune anti-cryptococcal

rabbit serum. Such tests have demonstrated fungous antigen in the cerebro-spinal fluid, blood and urine of a patient suffering from torula meningitis.

The early work dealing with the immunology of the systemic mycoses was bedevilled by the occurrence of cross reactions between antigens of the various antigens of the various pathogens concerned. This problem was largely solved by proper standardization and purification of fungal extracts, with the result that valuable procedures, best exemplified in the case of coccidioidomycosis, became available. Not only do certain pathogens show antigenic cross reactions, but these may also occur between pathogenic and saprophytic fungi. Using fungous extracts of sufficient concentration, common antigenic determinants have been found in *Aspergillus*, *Trichophyton*, *Cladosporium* and *Penicillium* species (Pepys, Riddell and Clayton, 1959). Precipitins against antigens of these fungi were demonstrated in human sera by the Ouchterlony agar-gel diffusion technique. This observation appeared to have significance in the investigation of aspergillosis and ringworm and possibly in the study of the subcutaneous mycotic infections.

There is little that can be said at this stage about the immunology of the subcutaneous mycoses. In chromoblastomycosis, immunological studies have not proved useful. In maduromycosis also they have not so far proved reliable for diagnosis. However, serological studies have indicated that the various causative fungi, *Monosporium apiospermum*, *Madurella grisea*, *Madurella americana* and *Glenospora clapierei* have distinct antigenic properties, and it is possible that such techniques may yet prove valuable both for diagnosis and for epidemiological survey work. Precipitins and complement fixing antibodies have been recorded irregularly in the sera of patients suffering from sporotrichosis. It has been suggested that this may be due to the small numbers of *Sporotrichum schenckii* yeast cells responsible for the localized lesions most typical of this disease. The somewhat greater success of immunological studies in sporotrichosis might be explained by the fact that *S. schenckii* is a dimorphic fungus with consequently greater potentialities for invasion.

Aspergillus fumigatus may produce disease in one of three ways:

(i) As an allergen in asthma and other allergic conditions.

(ii) As an allergen in pulmonary eosinophilia.

(iii) As an invasive pathogen in lung tissues, sometimes disseminating. The demonstration of precipitins against *A. fumigatus* in human sera has proved of value in determining the significance of this ubiquitous fungus in sputum (Pepys, Riddell, Citron, Clayton and Short, 1959). Skin testing with fungous extract may give rise to immediate-type hypersensitivity reactions or to those of typical delayed type. Of particular interest is an intermediate Arthus reaction occurring in some patients known to have precipitins against *A. fumigatus*. In these subjects the immediate weal reaction was followed after an interval of three to twelve hours by a local swelling, sometimes extending

widely, with poorly defined central induration. Histologically the reaction was found to consist of an infiltration of eosinophil cells, quite unlike that which characterises the delayed-type reaction.

In ringworm infections, the large amount of immunological knowledge gained in experimental *Trichophyton* infections in animals by the classical work of Bloch, Jadassohn, and DeLamater and Benham has failed to lead to useful diagnostic procedures in man. In human disease, immunological studies in the past have been practically limited to skin tests with *Trichophyton* antigen (trichophytin). Even today this antigen has not been adequately standardized. The reactions it produces are usually of the delayed type but occasionally, and particularly in *Trichophyton rubrum* infections, an immediate response is recorded. Marcussen described the successful passive transfer of this hypersensitivity in man by injection of serum, indicating that reaginic antibody is involved. Furthermore, Sulzberger observed that injection of trichophytin into sensitive subjects might provoke asthma and rhinitis, reactions known to be associated with the presence of reaginic antibody. The demonstration of circulating antibodies against *Trichophyton* species by laboratory tests was achieved by Pepys, Riddell and Clayton (1959) in their precipitin studies.

From clinical and experimental observations it has appeared likely that penicillin contains antigens which cross react with those contained in *Trichophyton* species. Thus, local application of this antibiotic may provoke exacerbations in ringworm, and parenteral use may give rise to reactivation of a previous dermatophytid or to the appearance of vesicular eruptions around areas previously affected by ringworm. A close relationship between sensitization to penicillin and to *T. mentagrophytes* has been demonstrated in guinea pigs using skin tests and uterine muscle contraction tests. It was not altogether surprising, therefore, that common antigenic determinants were found in *Trichophyton mentagrophytes* and *Penicillium notatum* by agar-gel diffusion techniques.

In moniliasis, at the present state of knowledge, no reliance for diagnostic purposes can be placed upon skin tests with yeast cell suspensions (oidiomycin) nor upon serological investigations. Positive skin reactions and precipitating, agglutinating and complement fixing antibodies occur in a substantial proportion of the population whether or not *Candida albicans* can be isolated from the bronchial, alimentary, or genital tracts of subjects investigated. High antibody titres frequently occur in subjects in whom no apparent infection by *C. albicans* exists and no evidence is available which shows that a consistent rise in titre occurs during the course of an infection.

The existence of common determinants in antigenic extracts of various fungi as shown by precipitin tests may merely be a reflection of the crudity of these products. Critical evaluation by adsorption and inhibition tests, and by chemical characterization of purified antigens, may elucidate some of these problems. The possibility that more than one antigenic fraction from a

fungous pathogen should be used for skin testing and serological diagnosis, as is the case for histoplasmosis, has to be kept in mind. It remains to be seen whether the antigens of fungi causing keratinous and subcutaneous infections can be rendered sufficiently potent and specific. It is possible that were this to be achieved, the fungi responsible for these non-disseminating infections might still fail to give rise to immunological responses of a magnitude useful in diagnosis. Both of these factors may explain the past failures in torulosis. Immunological evidence has led to the suggestion that hypersensitivity to *A. fumigatus* plays an important part in the production of pathological manifestations due to this organism. The better understanding was a direct outcome of the availability of an effective antigen. It is to be hoped that similar advances will follow in other common fungous infections.

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FAUN TAIL (SACRAL HIRSUTIES) AND DIASTEMATOMYELIA.*

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THE essence of the art of medicine is the acquisition of experience from personal observation, and that of others, so that small departures from normal form and function may be interpreted in terms of underlying, bodily disorders, to the benefit of the patient. It is our purpose here to draw attention to such a correlation which, though it has been observed and recorded by others, is not so well or so widely recognized as it ought to be.

From time to time patients appear at dermatological or other clinics with an abnormal growth of hair on the skin of midline of the back. It is usually in the sacral region (Fig. 1) but may be found in lumbar (Fig. 2), thoracic or even cervical areas. It seems to be visible in the earliest months of life (our youngest case was aged six weeks) and females predominate over males in a proportion of about four to one. As it happens, the ten cases described in this paper are all female. Sometimes the abnormal growth of hair is the sole reason for seeking medical advice, at other times it is a chance observation in the course of examination for other reasons.

Darier (1923) observed the condition and recorded it in the following terms. "*Parfois l'hypertrichose prédomine à la région sacrée, y formant cette touffe dont les anciens ont fait un attribut des faunes*". From this we derived the name "faun tail" for the external component of this clinical condition.

It is reasonably well recognized that this congenital abnormality, in common with several other skin changes found on the back, such as haemangiomas, pigmented moles, fat pads, sinuses or dimples, may indicate underlying spina bifida. With meningocele, of course, the association is obvious. However, less well recognized is the occasional complication to which Andrews (1954) drew attention, viz. diastematomyelia. Neurologists and neurosurgeons have linked the two together for some time but most of their cases have been those where attention was drawn to the spinal defect by the onset of organic neurological disorder. It is our purpose to show that such disastrous (because frequently irreversible) changes may be anticipated and averted.

* Based on a paper read on 8 July 1960, at the Franco-British Reunion in London.

Diastematomyelia was first described by Ollivier in 1837 who had observed it *post mortem*. It consists of duplication or splitting of a portion of the spinal cord. Through the apperture so formed there passes a bony spur or fibrous band attached anteriorly to the vertebral body or posteriorly to a remnant of the neural arch, or both (Fig. 3). The relationship may be likened to that of collar stud and collar. In the course of normal growth in childhood and adolescence, the relative lengthening of spinal cord and column is not precisely



FIG. 1.

proportionate. Thus there is a sliding movement of one within the other and a given point on the cord may alter position relative to the spinal column by as much as two vertebrae. Manifestly, a cord which is transfixated in this way must sustain damage from such a shift and this is in fact what occurs.

The child may fail to walk, or, having begun to do so normally, then begins to stumble or to drag one foot. The patient may also have scoliosis or deformity of the chest due to congenital abnormalities of the spine and ribs. A meningocele is often associated with diastematomyelia and, if the former can be repaired, the child may survive to fall a victim to the latter. In the later stages, the Arnold-Chiari malformation may be produced with resultant hydrocephalus

and blindness. Should the condition not be detected and dealt with surgically in time, the major paresis may develop with permanent, irreversible crippledom. One of us (W. R. R. T.), while working in Canada saw a number of such tragic cases in an institution for the permanently disabled.

Radiologically the cases fall into three diagnostic groups :

(i) In these the diagnosis can be made easily from an antero-posterior view of the dorsal and lumbar spine. This shows fusiform widening of the spinal canal with a midline shadow which represents the bony spicule seen end on



FIG. 2.

(Figs. 4 and 5). The lower dorsal or lumbar spine is usually involved. This may be shown clearly by tomograms when the appearance on plain films is indefinite. The pedicles are of normal appearance and not flattened as would be the case with an expanding lesion in the spinal canal. The exception to this rule is a dermoid cyst within the spinal canal which may result in pressure erosion of the pedicles. The diagnosis is certain in this group but a myelogram should always be performed to forewarn the neurosurgeon of a dermoid cyst.

(ii) In the second group, diastematomyelia can with equal certainty be excluded as the spinal canal is not significantly widened, no bony spicule is present and congenital anomalies are usually of minor degree.

(iii) In the third group, a spicule often cannot be identified with certainty because the congenital deformities of the spine are very gross and widening of the spinal canal from abnormal causes is difficult to distinguish from the normal lumbar widening at this level. In the absence of the spicule, widening of the

interpedicular distance is non-specific. It may be encountered with gross spina bifida, meningocele, posterior enteric remnants and hypertrophy of the filum terminale. Myelography is essential in this third group to show division of the contrast column around the septum. A larger quantity of contrast medium than usual is needed in these cases as the canal is wider than in normal children and the contrast column tends to break up into a large number of droplets. The column usually divides into two more or less equal limbs (Figs. 6 and 7), but one channel may be much smaller than the other and fail to fill completely.

Surgery is essentially prophylactic and should be performed as soon as the

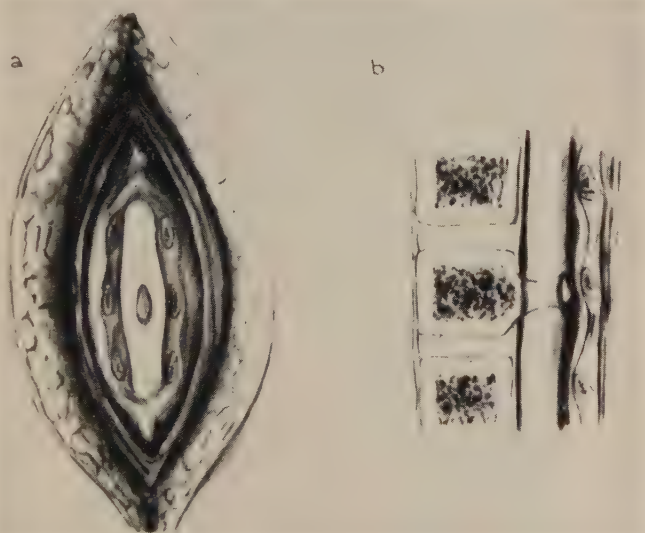


FIG. 3.

diagnosis is made even if no symptoms have developed. Symptoms may first appear when the child should normally be beginning to walk or as late as the early twenties, but in the majority of cases they are manifest before the age of ten years.

Finally, we would like to stress that this is a relatively common condition. We have seen about twenty-five cases over a period of five years. The neurosurgical procedures it necessitates are of considerable complexity and delicate precision, and such details are outwith the scope of this paper. Suffice it to say that the object is to remove the bony or fibrous spur which transfixes the cord without leaving a rough surface on the vertebral body and without damage to cord, spinal nerve roots or investing membranes. If the cord has sustained damage before or unavoidably at operation, physiotherapy may be required to restore function.

CASE REPORTS.

It may be of interest to provide brief clinical and radiological details of ten cases we have encountered. All were in girls.

Case 1.—First seen in Isle of Wight in 1952, aged 2 years. X-rays then and more recently show only spina bifida occulta. Growth and development have been entirely normal except for moderately severe constipation all her life.



FIG. 4.

Case 2.—Aged 10 years when first seen in the Isle of Wight in 1954. X-rays showed simple, moderate spina bifida occulta. Not further investigated. When first seen, the "tail" was fully 6 inches long. Normal healthy growth observed on follow-up. Last seen in July, 1959. Hair on sacrum then reduced to between 1 and 2 inches in length.

Case 3.—Aged 8. First seen in Portsmouth in March 1959, because of sacral "faun tail". No other clinical deformity of back but X-rays revealed a faint bony spicule in the midline typical of diastematomyelia and other associated spinal deformities. Dr. Moseley of Portsmouth Paediatric Department examined her and found some wasting of left leg and abnormally brisk reflexes on that side. She was referred to the Neurosurgery Department, Hospital for Sick Children, Great Ormond Street, London, (Mr. Till). The presence of diastematomyelia was confirmed by myelogram and successful surgical removal of the bony deformity was carried out. She had a little difficulty in walking during convalescence but physiotherapy dealt with this and she is now in every way fit and well.

Case 4.—In July 1959, the school medical officer, who had referred Case 3, spotted this 5-year-old girl with a mild faun tail. X-rays revealed a moderate spina bifida but there was nothing more clinically or radiologically to warrant further investigation. She is, however, being kept under observation.

Case 5.—Aged 5. This case was seen in Winchester in late 1959. Knowing our special interest in the subject, colleagues there kindly allowed us access to the case notes, X-rays and photographs. A particularly thick faun tail was present. X-rays revealed changes typical of diastematomyelia. In the hands of Mr. Till of Great



FIG. 5.

Ormond Street, a myelogram confirmed the latter, and successful operative correction was performed.

Case 6.—Aged 6 weeks. Tuft of hair and small, flat haemangiomata on skin of sacral area observed shortly after birth. X-rays showed "obvious widening of the interpedicular distance . . . little doubt that diastematomyelia is present". Operated on by Mr. Till at three months. "A firm growth of the filum terminale was partially removed, leaving the fragments attached to the conus." This has been reported by two pathologists as an ependymoma and a lipoma respectively.

Case 7.—Aged 19 years. Consulted her doctor purely on cosmetic question of whether prominent sacral "faun tail" could be removed. Referred to skin clinic. Obvious clinical spina bifida but X-rays showed no other abnormality. Diminished vibration sense lower limbs. On follow-up list.

Case 8.—Aged 6 years. Referred to Southampton Children's Hospital because of defective gait of about 4 years' duration. Clinical examination showed left leg to be

thinner and shorter than the right. Faun tail present in sacral area and upper end of natal cleft deviated slightly to the right. X-rays showed widening of interpedicular distance maximal at level L3-4. No definite bony spicule. Combined X-ray and clinical findings are here considered to warrant further investigation in the form of myelogram in a neurosurgical department. She has been referred for this ; result not yet available.

Case 9.—Aged 12 years. Referred to Paediatric Department, Portsmouth. Classical sacral faun tail. No complaints concerning function or sensation of lower limbs. Neurological examination negative. X-ray report: spina bifida of L5 and sacrum is



FIG. 6.

“open”. No undue separation of pedicles or bony spur to suggest diastematomyelia. No further investigations at the moment considered necessary but patient is to be kept under periodic observation.

Case 10.—Aged 4 years. Referred to Skin Clinic, Cosham, because of sacral tuft of hair and haemangioma. Mother gave history that two previous children had been born with other congenital deformities (hare lip, cleft palate, etc.) and did not survive beyond first few months of life. Full neurological examination revealed no abnormality of function or sensation. X-ray report : some widening of lumbar spine, L2-3, and failure of fusion of neural arches L2, 3, 4 and 5. Myelogram report : contrast medium flowed without obstruction through the lumbar and dorsal region. The sub-arachnoid space terminated at lower border of L5 (higher than normal). No definite evidence of diastematomyelia but there might be a small spicule at level of body of L2. Laminectomy not considered justifiable but case to be kept under observation.

Because of congenital deformities in previous children, mother insists on plastic operation to remove faun tail.

Commentary on Cases Presented.—All were in females, mainly of fair complexion. Ages ranged from six weeks to nineteen years. Spina bifida present in all. Definite diastematomyelia in four and probably present in a further one (Case 8), which is still under investigation. Three of the positive cases have so far undergone laminectomy and successful surgical removal of the abnormal spinal canal contents.



FIG. 7.

DISCUSSION.

The exact mechanism of this congenital disorder is a fascinating field for speculation. One theory is that it is in some way linked up with certain forms of pilonidal sinus, i.e. a fault in the embryological in-folding of the neural plate of ectoderm which forms the central nervous system. A second postulate is that the localized or, rarely, extensive duplication of the cord is either an abortive attempt at twinning or an atavistic throw-back to some primaeval stage in evolution in which the central nervous system was duplicate, like that of coelenterates. Thirdly, it may be a neuro-enteric remnant as suggested by Bremen (1952) and, on the whole, this seems to us to be the likeliest explanation.

Matson *et al.* (1951) described a series of eleven cases treated surgically, of

which nine were diagnosed pre-operatively. Ages ranged from eight weeks to five years, nine months, with an average of two years eight and a half months. Seven were female and three male. No external cutaneous defects were present in two cases. In the others the following were seen : lipoma only, 2 cases ; tuft of hair only, 1 case ; tuft and haemangioma, 2 cases ; dimple only, 2 cases ; dimple and lipoma, 1 case ; dimple and tuft, 1 case. Perrett (1957) reported 5 cases of which four were female and one male. Four cases showed the dorsal faun tail tuft of hair and the fifth a meningocele. Ages ranged from one month to three and a half years, with an average of fourteen months. Neuhauser *et al.* (1950) brought the total of cases of diastematomyelia reported at that time up to forty-two and discussed the radiological features of Matson's cases. In this country, the radiological aspects were also described by Cowie (1951 and 1952).

Grateful acknowledgement is made to various kind friends and colleagues who have helped in the production of this paper. In particular we wish to thank Dr. J. H. Moseley—Cases 2 and 9, Dr. G. Ormiston—Cases 5 and 8, Dr. P. R. Montgomery—Cases 5 and 10, Mr. K. Till for surgical notes, Cases 3, 5 and 6. Fig. 3 is reproduced from Caffey's *Pediatric X-ray Diagnosis* by permission of the Year Book Publishers Inc., Chicago.

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THE HISTOCHEMICAL LOCALIZATION OF PHOSPHORYLASES IN SKIN.*

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WE are concerned here with the intracellular storage and mobilization of carbohydrates in the skin. Generally speaking, glucose can diffuse into and out of the cell, and when it is needed for these biochemical processes it is held within the cell first as a glucose phosphate. Thus glucose is esterified at the cell membrane under influences which include hexokinase and A.T.P. (adenosine triphosphate), and the resulting glucose-6-phosphate will remain inside the cell and can be further metabolized. An enzyme (phosphoglucomutase) may then switch the phosphate group to the C1 position resulting in a glucoside glucose-1-phosphate and this is the raw material for our histochemical reactions (the building up of glycogen).

Starting with glucose-1-phosphate, plant and animal cells build up polysaccharides under the influence of enzymes which are called transglucosidases or phosphorylases. The first step is the condensation of glucose units into straight chains of amylose through C1-C4 linkages, with elimination of phosphate (transglucosidation) and the enzyme necessary for this is amylophosphorylase (in plants this is called "P enzyme"). These amylose chains can be built up further under the influence of another transglucosidase (branching enzyme) through C1-C4 to C1-C6 linkages, giving high polymer branched molecules. In plant cells the branching enzyme is called "Q enzyme" and catalyses the formation of pectins. In animal cells the branching enzyme leads to glycogen formation. The term "phosphorylase" is often loosely applied to both transglucosidase activities (amylophosphorylase and branching enzyme). This usage is followed in this paper, though it is not strictly correct (Pearse, 1960).

These transglucosidases are also concerned with intracellular breakdown of polysaccharides; in other words the reaction goes both ways. Outside the cell, digestive enzymes (amylases) break down glycogen and amyloses. Takeuchi (1958) has used purified amylases as an aid to distinguishing the types of polysaccharides that are synthesized in the histochemical reactions we are about to consider.

In recent years the work of Leloir and Cardini (1957), has led to great interest in the role of uridine diphosphate glucose in glycogen metabolism. This nucleotide acts as a co-enzyme in the conversion of glucose-1-phosphate to

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glycogen; and similar nucleotides are important in a variety of polysaccharide building reactions. This pathway is an alternative to the amylophosphorylase pathway already mentioned.

The biochemists have shown these glycogen-building enzymes to be present in muscle and liver, for example, and Takeuchi (1955, 1956) has elaborated histochemical methods whereby the activity of these enzymes can be indicated in animal tissues. In all cases we use simple means for demonstrating the final products of enzyme action which are polysaccharides, for example the PAS reaction, or better the iodine reaction. Takeuchi's work in this field has led to recognition of different colours with iodine for different polymers (blue-black for amyloses and purplish to brown and red for glycogens).

MATERIAL.

In all cases, fresh skin has been used. A few minutes in a fixative such as formalin will destroy the transglucosidases. Most of our material has been from biopsies of adult human skin made under local anaesthesia, but surgical specimens have been obtained in some cases where local anaesthetics have not been used. While much pathological material (particularly tumours) has been examined, we shall limit this report to normal skin. We have also studied skin from various sites in mice, guinea-pigs, cats and monkeys.

METHODS.

The fresh specimen of skin is immediately frozen on to the chuck of the microtome and kept frozen in CO₂ ice until sections are cut. The Pearce cold microtome (cryostat) has been used for cutting sections at -18°C . and for most of this work we have used a thickness of about $25\ \mu$. The frozen sections are allowed to dry on to coverslips for some hours in the cold cabinet of the cryostat, before they are placed in the incubating medium.

We have used the method of Takeuchi (1958) and recently we have included the modifications suggested by Goltz *et al.* (1959).

To the substrate, glucose-1-phosphate in acetate buffer (pH 5.8) is added a primer, glycogen. Adenylic acid, insulin, and magnesium ions are added as activators. Incubation is carried out at room temperature for one hour. Control sections are incubated in a medium identical except for the omission of glucose-1-phosphate and adenylic acid. After incubation, sections are briefly fixed in alcohol before adding dilute Gram's iodine in order to develop the polysaccharide colours. Comparison is made between controls and sections incubated in the substrate proper. The sections must be assessed immediately, as the iodine colour fades after a few hours at room temperature. In practice the controls show little or no iodine reaction unless much preformed glycogen is present in the tissue.

Takeuchi's method for uridine diphosphate glucose pathway.—In a few cases we carried out the procedures described by Takeuchi and Glenner (1960) using specimens that contained muscle as well as skin (facial skin close to the lip).

RESULTS.

Variations in Positive Results.

We have found with these histochemical methods rather marked variations in transglucosidase activity of skin even when taken from comparable sources.

It is difficult always to ensure the same degree of freshness of tissues and furthermore some inhibition may be attributed to local anaesthetics. We find that lignocaine added to the incubating medium inhibits transglucosidases in final concentration of 1%, but has no effect at final concentration of 0.1%.

Some variations between sections from the same block may be attributed to minor differences in handling, for instance, sometimes it is difficult to cut sections of uniform thickness. Variations in histochemical reactions may also occur in different parts of the same section, even allowing for the anatomical points mentioned below such as proximity to follicular or ductal opening. Sometimes differences are hard to account for and we have to allow for some vagaries of the method. In interpretation and comparison of results, fading of the iodine polysaccharide colour at room temperature must be remembered.

The results refer to normal adult human skin unless otherwise stated. Only a brief outline of transglucosidase activity patterns is given, as other workers have already published adequate descriptions (Braun-Falco, 1957; Ellis and Montagna, 1958; Goltz *et al.*, 1959).

Epidermis.

Amylophosphorylase and branching enzyme activities are demonstrable in the epidermis with variations between specimens, depending on species, age and skin site. Strongest phosphorylase activity is usually detectable in the basal layer, but some activity may be noted throughout the prickle cell layer but not in the stratum corneum. Individual basal cells may show strong phosphorylase activity in contrast to their neighbours. Very nearly all phosphorylase activity appears to be cytoplasmic, but in some epidermal cells the nucleolus is positive.

Regional differences are marked. The thick epidermis of palm and sole shows much phosphorylase activity and the epithelium of the vulva shows more still. On the other hand, the surface epithelium of the tongue and the buccal mucosa show weak phosphorylase activity. In hair-bearing skin, the epidermis usually shows rather weak phosphorylase activity, whereas smooth skin such as eyelid or ear, even though thin, may show a fairly strong reaction. Often the basal and suprabasal layers of epidermis immediately around the point of entry of a hair follicle or sweat duct show much more phosphorylase activity than the intervening epidermis (the same is true for pre-formed glycogen, as seen in ordinary fixed sections).

Cornea (Adult Guinea-pig and Rhesus Monkey).

Corneal epithelium shows a very strong transglucosidase activity whereas the substantia propria and endothelium are negative.

Pilosebaceous Follicle.

Both amylophosphorylase and branching enzyme activities are shown strongly in the external root sheath.

The Sebaceous Gland.

Phosphorylase activity is shown in its marginal basal cells.

The Pilo-sebaceous Duct.

This shows transglucosidase activities similar to surface epithelium but stronger.

Eccrine Sweat Unit.

Amylophosphorylase activity is very strong indeed throughout all epithelial cells of the unit, both secreting and ductal. Branching enzyme does not seem to be present. The luminal cells of the epidermal part of the sweat duct show strong amylophosphorylase activity.

Aprocrine Sweat Unit.

No transglucosidase activity is found in the epithelial cells of the apocrine gland. The apocrine sweat duct is strongly positive for amylophosphorylase and similar to the eccrine sweat duct.

Myoepithelial Cells.

These cells are best seen in the apocrine gland since the secreting epithelium by contrast shows no transglucosidase activity. The delicate myoepithelial

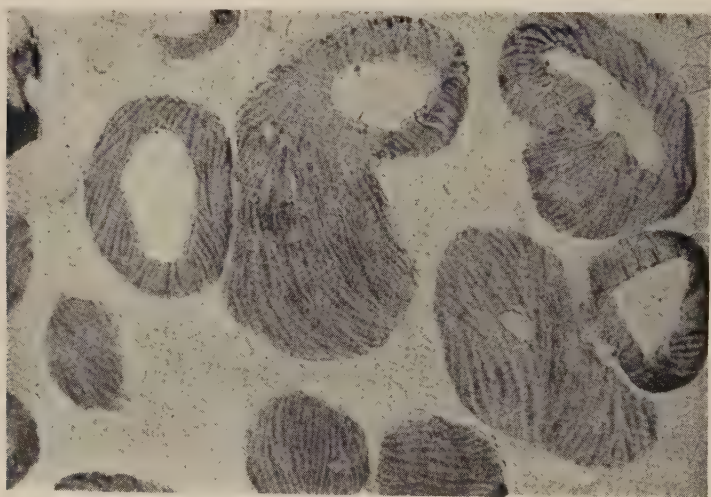


FIG. 1.—Apocrine gland from human vulva. Amylophosphorylase activity in myoepithelium. Secreting cells are negative for transglucosidase activity.

fibres show up clearly with the reaction for amylophosphorylase. Their morphology is shown rather beautifully with this histochemical method, the fibre strands wrapping the gland rather like the turns on a ball of wool (Fig. 1). The myoepithelium of eccrine glands can sometimes be made out, but with

difficulty because the secreting epithelium is so strongly positive for amylophosphorylase.

Blood Vessels.

Muscle fibres in the walls of arteries and veins show a positive reaction for amylophosphorylase.

Pilo-motor Muscle.

This and other muscle fibres, if present in the skin, show amylophosphorylase activity.

Nerve Bundles.

Some areas of rather weak phosphorylase activity are apparent.

Uridine Diphosphate Glucose Pathway.

With this method we find the epithelial structures of the skin to be negative throughout. Muscle bundles deep in the skin and subcutaneous tissue (human lip) show the red-brown colour of the positive reaction as described by Takeuchi and Glenner (1960).

EXPERIMENT.

Leaving normal skin, we thought that it would be of interest to examine several situations in which an increase of glycogen can be induced. One of us (K. V. S.) is working on this problem in the skin of laboratory animals, studying the induction of the hair cycle by plucking, and the changes induced by oestrogens in the nipple and female genital tract and this work will be reported elsewhere. The other situation which we can exploit is the epidermal regeneration which occurs after stripping off the keratin from the human skin surface. Glycogen cannot ordinarily be demonstrated in the basal layer of the epidermis though variable amounts accumulate in the prickle cells more distally. Lobitz and Holyoke (1954) showed that about 8 hours after stripping off the keratin, glycogen appears in the basal cells, and it disappears before these cells go into mitosis (at about 48 hours).

Two adults male volunteers were used. An area 2 cm. by 14 cm. on the flexor aspect of the forearm had the keratin removed by 30 to 40 pulls of cellophane tape, until a uniform red shiny surface was produced (Pinkus, 1952). Serial 5 mm. punch biopsies were made at 10 minutes, 4, 8, 28 and 52 hours following the keratin stripping. One per cent lignocaine was used as local anaesthetic. Biopsy specimens were halved and one half of each was fixed in 10% calcium formalin and paraffin sections were made and stained for glycogen. The other half of each specimen was immediately frozen in CO₂ ice, after which frozen sections were made and these were processed for transglucosidases.

RESULTS.

The histochemical results were approximately the same in the two series of biopsies.

At 10 minutes and 4 hours there was phosphorylase activity in the mid-

prickle cell layer and in the basal-cell layer and this activity was about the same as in normal skin. At 8 hours the phosphorylase activity was stronger in the basal cell layer (Fig. 2*a*) and in some cells just above the basal layer. At 28 hours (preceding mitosis) and at 52 hours (numerous mitoses) very little transglucosidase activity could be detected in the epidermis (Fig. 2*b*) and it was less than in normal epidermis.



FIG. 2*a*.—Eight hours after keratin stripping (glycogen phase). Strong transglucosidase activity in cells of the basal and suprabasal layers of epidermis.

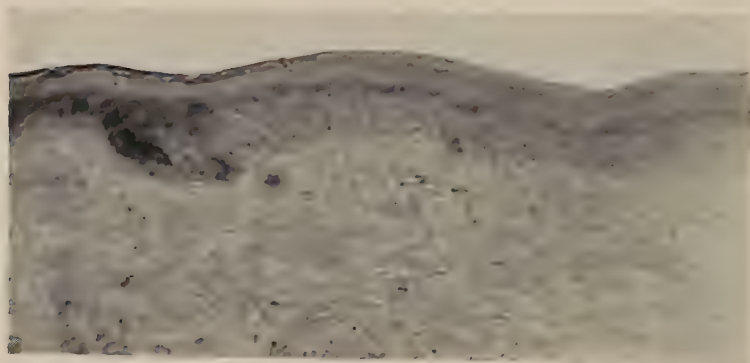


FIG. 2*b*.—Fifty two hours after keratin stripping (mitotic phase). Minimal transglucosidase activity in the epidermis.

DISCUSSION.

Others who have used these histochemical methods for demonstrating transglucosidases in skin (notably Braun-Falco, 1957; Ellis and Montagna, 1958 and Goltz *et al.*, 1959) have reported some correlation between transglucosidase activity and the presence of glycogen as shown by ordinary histochemical

methods, while at the same time noting exceptions to this relationship. Our experience confirms these observations. There is an apparent correlation between abundant glycogen in the external root sheath of the hair follicle and the presence of amylophosphorylase and branching enzyme. The eccrine sweat gland has much glycogen in its secreting epithelium, and the strong amylophosphorylase activity demonstrable here appears to be directly associated with it. On the other hand, the adult apocrine sweat gland shows little glycogen (Hurley and Shelley, 1960), and we can confirm that its secreting cells show no transglucosidase activity as reported by Yasuda *et al.* (1958) who emphasized this striking histochemical difference between the two types of sweat gland. While glycogen can often be found in the prickle cell layer of adult human epidermis, it is not normally present in the basal layer. Phosphorylase activity is usually strong in the basal cell layer, though present to a variable and lesser extent in the rest of the Malphigian layer. In the keratin stripping experiment a striking increase of glycogen may be observed in the basal cell layer 8 hours after stripping (Lobitz and Holyoke, 1954) and there seems to be a corresponding increase in phosphorylase activity about this time. It disappears later on in the premitotic phase of epidermal regeneration.

Previous workers have failed to show any transglucosidase activity in adult laboratory animal epidermis and have even gone so far as to suggest a different metabolic pathway from human epidermis (Ellis and Montagna, 1958). We have studied adult mammalian skins and have found transglucosidases to be present in epidermis, though there are marked regional and species variations. We think it unlikely that the metabolic pathways are qualitatively different and propose to publish more detailed observations on animal skin. The high glycogen content and strong phosphorylase activity of very young skin has already been reported (Takeuchi, 1958).

In the adult, the epithelia tend to have a variable transglucosidase activity and certain sites such as the vulva show very strong activity; here a close correlation with glycogen is apparent. We were interested to find strong phosphorylase activity in the corneal epithelium (guinea-pig and monkey) and this can be considered in relation to knowledge of the biochemistry of the cornea (Pirie, 1960) with glycolysis predominating over oxidation of glucose.

We must note, however, that there are some sites where strong phosphorylase activity can be shown histochemically, but where glycogen does not accumulate to any extent. The ducts of the sweat units, both eccrine and apocrine, have very strong amylophosphorylase activity, but little glycogen. There is some uncertainty as to how much glycogen is normally present in sweat ducts and in the apocrine gland. Hurley and Shelly (1960) take the generally accepted view that there is only very little glycogen at these sites, whereas Montagna *et al.* (1951) reported abundant glycogen in the apocrine gland and easily demonstrable glycogen in the sweat ducts. It should be remembered that the

histochemical methods available for demonstrating glycogen show only part of the glycogen actually present [that part which can be extracted with trichloroacetic acid (Kugler and Wilkinson, 1960)].

We are left with uncertainty as to the significance of amylophosphorylase at certain sites and particularly its relation to glycogen. Goltz *et al.* (1959) discuss the significance both of glycogen and of phosphorylase in epithelial tumours with particular reference to anaerobic glycolysis and to the process of keratinization. We find transglucosidase activities in epidermal tumours to be very variable and it appears that further work in biochemistry is needed in this very interesting field, before these histochemical findings can be properly interpreted. The variability of phosphorylase activity in different parts of one section refers particularly to the epidermis. While much of this variation may be related to technical difficulties as already mentioned, certain differences may be biochemically significant. In Fig. 2*a* for example, certain basal cells appear dark on account of strong phosphorylase activity, in contrast with other basal cells which show minimal activity. The impact of the stimulus of keratin stripping is unevenly spread to individual cells or groups of basal cells, so that they do not all build glycogen or go into mitosis at exactly the same time. Variations in phosphorylase activity may be noted in comparing one muscle bundle with another, and there is said to be reciprocity between phosphorylase activity and oxidative enzyme activity (Dubowitz and Pearse, 1960).

With uridine diphosphate glucose substrate, we were able to demonstrate glycogen synthesis in muscle but not in epithelial structures of the skin. Takeuchi (1960) has reported positive reactions in liver and muscle but negative reactions in the collecting tubules of the kidney. These results may indicate important differences in metabolism between muscle and epithelia; but at present our experience with this method for the uridine diphosphoglucose pathway is limited.

While on the subject of muscle, we think that our demonstration of amylophosphorylase is helpful in depicting the myoepithelium which wraps the apocrine gland and it seems to add to the evidence that Hurley and Shelley (1960) have already assembled in favour of this myoepithelium having the properties of contractile muscle.

SUMMARY.

The histochemical localization of transglucosidases (amylophosphorylase and branching enzyme) in skin is reviewed.

The positive amylophosphorylase reaction in the myoepithelium of apocrine glands serves to illustrate the morphology of the myoepithelial fibres.

With uridine diphosphate glucose substrate, the Leloir pathway for glycogen synthesis could be demonstrated in muscle but not in epithelial structures.

After keratin stripping, the accumulation of glycogen in the basal region of the epidermis was accompanied by increased transglucosidase activity.

We wish to thank Dr. J. A. Dudgeon and the Glaxo Laboratories Ltd., Greenford, Middlesex, for supplies of fresh monkey skin. We are grateful to Mr. R. J. Lunnion of the Institute of Dermatology for the photomicrographs.

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 YASUDA, K., FURUSAWA, H. and OGATA, N. (1958) *Okajimas Folia anat. jap.*, **31**, 161.

ROYAL COLLEGE OF PHYSICIANS

A conference is to be held at the Royal College of Physicians on Friday, 17 October 1961 at 2 p.m., devoted to skin disorders in relation to malabsorption and malnutrition. It is primarily arranged for Fellows and Members of the College. Numbers may have to be limited and application should be made to the Registrar, Royal College of Physicians, Pall Mall East, London, S.W.1, not later than 22 September 1961. Registration fee: 10/-; dinner: £2. Cheques should not be sent with the applications but become due on notification from the College. The provisional programme is as follows.

Chairman – Sir Robert Platt, Bt., P.R.C.P.

President's opening remarks.

Parkes Weber Lecture – *Skin disorders in Relation to Malabsorption and Malnutrition*. (Dr. G. C. Wells)

Starvation, Stress and Cell Replacement. (Prof. W. S. Bullough)

Nutritional Changes in the Oral Mucosa. (Prof. L. J. Witts)

Skin Changes in Hypocalcaemia. (Dr. M. Garretts)

Discussion.

Dinner.

OBITUARY.

DR ALBERT TOURAINE.

Albert Touraine was born in Paris in November 1883 and died in May 1961. He was educated at the Lycée Charlemagne in Paris, entering the Hôpitaux de Paris as an external student near the beginning of the century. In 1911 he was awarded the Gold Medal for Internes of the Hôpitaux de Paris. From 1912 until the beginning of the Great War he was a *Chef de Clinique* in the Faculty of Medicine of Paris. From 1914 to 1916 he served as Medical Officer to an infantry regiment in the Verdun area and for the remainder of the war as the specialist in charge of a dermatological and venereal Centre at Besançon. In 1919, in recognition of his military service, the distinction of *Chevalier* of the Legion of Honour was conferred on him while later in his life he was promoted to *Officier* and finally *Commandeur*.



He was Physician to the Hôpital St. Louis from 1932 to 1948 and during this period he performed not only the teaching and other duties of Physician-in-Charge of a *service* of the hospital but served on a considerable number of important public commissions and committees. In addition he was at various times Vice-President of the French Society of Genetics, President of the French National Anti-Venereal League, the Administrative Council of the Fournier Institute, and the National Syndicate of French Dermatologists and Venereologists. From 1939 to 1943 he was President of the French Society of Dermatology and Syphilography, remaining thereafter Honorary President until he died. Finally in 1960 he was made Vice-President of the Academy of Medicine.

Touraine thus performed much public service for his country. The remarkable fact is that at the same time he was one of the greatest contributors in the world to medical literature, matching in that respect our own Parkes Weber. He wrote particularly on genetic medicine on which he was recognized all over the world as a leading authority. Altogether his publications number about 1200 and these include

two books, an early treatise on haematology and a recent large work on heredity in medicine ; he also contributed a large number of chapters to various works on general medicine and dermatology. He was Editor-in-Chief of the *Annales de Dermatologie et de Syphiligraphie* from 1943 until he died.

Touraine first became acquainted with this country when he came to London to deliver the Prosser White Oration for 1953, a memorable occasion in which he readily won the admiration and warm regard of his British colleagues. He was naturally respected for his immense industry and erudition and for his intellectual integrity, but he perhaps won even more admiration for his natural humour and warm-hearted friendliness. Those who became better acquainted with him learned that he was what he appeared to be, a conservative Frenchman, devoted to his family and deeply attached to the traditions and well tried institutions of his country. He was elected an Honorary Foreign Member of the British Association of Dermatology in 1953.

Though his death will be greatly regretted on this side of the Channel, it is pleasant to think that his was an honoured name during his lifetime, not only in his own country but all over the world.

G.B.D.

BOOK REVIEWS.

THE FRENCH ENCYCLOPAEDIA.†

THIS further volume contains an adequate account of the histology and histochemistry of the skin and one giving the French approach to the *eczematides*. There is a first-rate description of *dyschromies* by Woringer and an interesting section on Paget's disease by Huriez with illustrations and diagrams of the underlying tissues in addition to the skin. The section on urticaria is unsatisfactory and makes no mention of heat urticaria and Grant's work on cholinergic urticaria and the account of the treatment is very uncritical. Other subjects dealt with include acute vesicular lesions, congenital bullous affections, granuloma annulare, systematized naevoid conditions and benign epithelial tumours. There are some beautiful coloured plates but as usual English names suffer badly, e.g. Radcliffe and Crocker. F. F. H.

THE FRENCH ATLAS.*

In the nineteenth section the illustrations conform to the high standard one has come to expect in this atlas. Perhaps particular mention should be made of the picture of acrodermatitis enteropathica with its representation not only of the cutaneous lesion, but of the demeanour and personality of the patient. The text includes excellent monographs on acanthosis nigricans, acrodermatitis enteropathica and xeroderma pigmentosum. The more difficult topic of Melkersson-Rosenthal syndrome is considered with care and discrimination. From these authors one would expect a particularly valuable account of Gougerot's *trisymptome* and allied conditions. One must concede that disorders of this class are sometimes difficult to classify and more difficult to understand. In the present number this disorder and its relationship with other conditions which it resembles are exposed with admirable clarity.

The twentieth section has now been published and completes the atlas. It is, however, understood that supplements are likely to appear from time to time in the future and this indeed would be desirable. The atlas as it stands is an excellent production and has no equal. Even so, it is evident that illustrations have to be made from cases as they occur, and for this reason it is understandable that the atlas in its present form could be further augmented. Certainly there is no common disorder which is not adequately and beautifully illustrated. There are also included many uncommon and rare conditions. It is, however, hardly possible to reach a state of such completeness that every rare disorder finds full representation. Naturally, the collection of these rare conditions will take considerable time and we may therefore expect to see supplementary numbers at infrequent intervals.

As it stands, the atlas is a remarkable achievement and your reviewer has had occasion to mention before the high standard not only of the illustrations but also of the text. One's only misgiving is perhaps that the loose leaf form of publication may not be sufficiently robust for library use.

F. R. B.

† *Encyclopédie Medico-Chirurgicale*. (1960). Special Volume 39, Dermatology. Paris: Éditions Techniques.

* *Atlas de Dermatologie*. P. DE GRACIANSKY and S. BOULLE. Paris: Librairie Maloine, London: H. K. Lewis.

CURRENT LITERATURE

TREATMENT OF WARTS BY LOCAL INJECTION OF VITAMIN A. J. V. KLAUDER. (1960) *Arch. Derm., Chicago*, **81**, 253.

A commercial vitamin A solution was used for local injection of plantar warts. For small warts two injections at intervals of 5 days to 1 week were sufficient to cause disappearance, for larger warts (including mosaic warts) 4 or 5 injections were required. The amount injected varied from 0.1 to 0.4 ml. at one site to a total of 1 ml. at 3 or 4 sites. In all 31 patients were treated with only one failure. In one case a single wart recurred but disappeared with a second course. Similar treatment of warts of the fingers was indecisive and treatment of various other conditions was either ineffective or was not superior to traditional methods. J. K.

MALIGNANT PAPULOSIS WITH ATROPHY (DEGOS) FATAL CUTANEOINTESTINAL SYNDROME. R. NOMLAND and J. M. LAYTON. (1960) *Arch. Derm., Chicago*, **81**, 181.

PAPULOSIS ATROPHICANS MALIGNA (DEGOS'S DISEASE). D. NAYLOR, J. F. MULLINS and J. F. GILMORE. (1960) *Arch. Derm., Chicago*, **81**, 189.

Each paper records a male patient, one aged 25 and the other 55. Of 10 cases hitherto reported 9 have occurred in males. The disease starts with scattered papular lesions of the skin which in a few days change from pale red to porcelain white, umbilicated areas covered with a thin white scale. The lesions may enlarge for two to three weeks, the maximum size being 10 mm. across, and the periphery is very sharp, slightly elevated, rose-coloured and may show slight telangiectasia. After a period of weeks the lesion subsides and a white area of atrophy which is not a true scar remains. The eruption progresses by the appearance of new lesions, three or four at a time, at intervals of a few days or weeks. Several months after the onset of the cutaneous phase, intestinal symptoms develop, mild at first, but leading to an acute terminal episode with symptoms of general peritonitis with ileus. If laparotomy is done yellow atrophic patches scattered throughout the small bowel are found. Later perforations occur with areas of gangrenous bowel and general peritonitis. Similar lesions may be found in the brain, kidney and heart muscle. Biopsy of the skin shows occlusive endothelial proliferation of deep arteries while the superficial capillaries are dilated with moderate perivascular infiltrate. There is necrobiosis of a wedge shaped area of dermis with little surrounding infiltrate. The intestinal lesions show similar features.

It is suggested in the second paper that it is a form of necrotizing angitis but no definite etiology has been established. J. K.

THE NODULAR DERMAL ALLERGID : A TYPE OF ALLERGIC VASCULITIS. C. W. LAYMON. (1960) *Arch. Derm., Chicago*, **82**, 163.

The author describes a case and discusses the clinical and histological features of this condition, formerly known as Gougerot's trisymptomatic disease, characterized by small dermal nodules, erythematopapular elements and purpura. This condition is included in a group of diseases that vary greatly in their clinical pictures but have in common the microscopic features of inflammation of the arteries in various organs leading to haemorrhage followed by necrosis. If the arterioles and capillaries are affected there may be polymorphous cutaneous eruptions without interference with the general health. This includes certain cases of purpura, the nodular dermal allergid, and allergic arteriolitis (Ruiter). If medium-sized arteries of the skin are involved the term cutaneous periarteritis nodosa has been applied. If arteries in other organs are affected, various syndromes have been described showing a wide variety of clinical pictures usually of serious import and ending in death. These include periarteritis nodosa, Wegener's granulomatosis and temporal arteritis. Degos's disease starts with benign outbreaks of necrotic skin papules, a phase which lasts for a few weeks to a few years, but is succeeded by a second phase which begins dramatically with acute intestinal symptoms due to involvement of the intestinal arteries leading to necrosis, perforation, peritonitis and death. Allergic granulomatosis has an allergic background which is not found in the other conditions. The cause of the reaction is unknown and there is no satisfactory treatment. J. K.

DISSEMINATED XANTHOSIDEROHISTIOCYTOSIS (XANTHOMA DISSEMINATUM). K. M. HALPRIN and A. L. LORINEZ. (1960) *Arch. Derm., Chicago*, **82**, 171.

A man aged 45 had suffered for five years from gradually progressive muscular weakness and a disfiguring skin eruption. There was weakness and atrophy of the shoulder girdle and thigh muscles and an eruption on the face, chest and back; infiltrated, firm, brownish green plaques of bizarre shape. Biopsy of skin and muscle showed an infiltrate of large histiocytic cells which had absorbed fat and iron. The only notable blood abnormalities were reduction in serum lipids, phospholipids and cholesterol. Liver function tests, x-rays and electrocardiograms were all normal. After a steadily declining course he died less than two years later.

This case belongs to a group showing widespread benign histiocytic tumours. These histiocytes have absorbed fat and in this case iron but are otherwise histologically normal. Hyperlipaemia and hypercholesterolaemia are not present and thus cannot be blamed as a cause. The term "xanthoma disseminatum" implies a causal relationship between lipid metabolism and the lesions which probably does not exist. It seems preferable to consider the lesions as histiocytic proliferations which have secondarily phagocytosed fat and occasionally iron. The alternative name has therefore been proposed. There appears to be a relationship with histiocytoma cutis in which both clinically and histologically the lesions are indistinguishable from those of xanthosiderohistiocytosis but which runs a benign course. Reticulohistiocytoma seems to belong to the same group and in extent and severity occupies a position between the other two. Naevoxanthoendthelioma (juvenile xanthogranuloma) has quite special features and its relationship to the others is problematical. Reticuloendotheliosis (e.g. Hand-Schüller-Christian disease) differs from these conditions in that the cellular infiltrate is composed of more immature cells, and pleomorphism is always present to some extent. The picture borders on the malignant. The lesions rapidly respond to X-ray therapy which has no effect on the other conditions mentioned. J. K.

PITYRIASIS ALBA. B. T. WELLS, H. J. WHYTE and R. R. KIERLAND. (1960) *Arch. Derm., Chicago*, **82**, 183.

Pityriasis alba is common but the literature on the subject is limited. It is most frequent under the age of 15 and usually starts in summer or winter. There are somewhat fewer cases starting in spring and very few in autumn. The most consistent finding is excessive dryness of the skin from winter wind or summer sun. Hypopigmentation makes the lesions more noticeable in dark-skinned subjects. No bacterial or fungal cause is found, the condition tends to clear regardless of treatment which should be confined to bland lubricants. More energetic measures have little or no effect. J. K.

TREATMENT OF ERYTHRODERMIA FIGURATA VARIABILIS (TYPE MENDES DA COSTA) WITH VITAMIN A. K. WULF, H. KOCH and K. H. SCHULZ. (1960) *Derm. Wschr.*, **142**, 1012.

Vitamin A in a dosage of 100-150,000 international units daily with a maintenance dose of 50,000 units is recommended. Definite improvement in this rare and most intractable condition was achieved in two cases. J. M.

PEUTZ-TOURNAINE-JEGHERS SYNDROME. K. HARNACK. (1960) *Derm. Wschr.*, **142**, 1215.

Two cases are described in view of the paucity of published material in the German literature. Both were in women who showed pigmentation of lips, lingual and buccal mucous membranes. Polypi were present in the stomach and sigmoido-rectal junction and rectum. The "obligatory" dominant hereditary component is doubted: these two cases were sporadic. The author feels that dental surgeons might be encouraged to look out for changes on the oral mucosa. J. M.

TREATMENT OF LICHEN PLANUS WITH CHLOROQUINE. M. NIETZKI. (1960) *Derm. Wschr.*, **142**, 1223.

Two cases (bullous lichen planus and lichen plano-pilaris) were successfully treated. The daily dosage was 500 mg., later 250 mg. J. M.

PSEUDOPELADE WITH DIFFUSE HYPEROSTOSIS OF THE SKULL AND CONDENSING OSTEITIS OF THE ILEUM. O. DIETZ and G. SABINSKY. (1960) *Derm. Wschr.*, **142**, 1295.

The above changes together with a small sella turcica in a female patient aged 37 are described. The authors agree with Degos and Priolo that Pseudopelade is not a disease *per se* but a terminal stage and they postulate the possibility of endocrine factors playing a part.